Process Control Implementation in a Clinical Manufacturing Environment

by

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B.S. Biomedical Engineering, Johns Hopkins University, 2008

Submitted to the MIT Sloan School of Management and the Department of Mechanical Engineering in Partial Fulfillment of the Requirements for the Degrees of

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and
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Abstract

Amgen is shifting certain drugs from traditional vial and syringe primary containers to more patient friendly delivery devices known as combination products. Combination products are defined by the combination of a medical device and drug into a single entity. These new products are accompanied by new regulations and new production processes. Traditional drug manufacturers are required by the FDA to embrace certain practices traditionally pertinent to medical devices. As Amgen seeks to integrate these device processes into its business processes, additional quality procedures are necessary to control and improve the new production processes.

This thesis seeks to examine process control techniques in the clinical manufacturing organization in an attempt to understand and improve the current new processes. A control plan was developed based on risk inputs, observational run data, and batch release requirements. A data collection process was then implemented and data was analyzed in control charts and aggregated defect rate analysis. Results show that 1) the overall assembly process appeared to stabilize over the period of analysis, 2) although processes were within specification limits, none of the inspection processes were entirely within statistical control, and 3) investigative avenues for out of control processes are suggested as a part of the control feedback loop. Recommendations regarding managerial challenges in implementing a quality control system are also suggested.

The opinions expressed herein are solely those of the author and do not necessarily reflect those of Amgen Inc.

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Acknowledgments

I've always felt particularly special that, buried somewhere in a library vault, my name is on page 2 of my father's thesis. Now that I have the same opportunity, I find myself wanting to thank everyone who has supported me through my experience at MIT—and the list is long.

I would like to recognize Mike Schechter, Frank Ye, Pete So, and Leigh Hunnicutt for teaching and guiding my efforts at Amgen. Thanks to my fellow interns Aditya Nag, Sam Cosby, and Seth White for your ideas, opinions, and good company throughout my internship experience in Thousand Oaks. I'd also like to recognize the awesomeness of my LGO summer team and Sloan core team: mounting up with the Regul8tors has truly defined my LGO experience, and the Caribbean Gulls have been the best core team a girl can have.

Above all, I would like to acknowledge my parents, Raj and Ranga, for always providing unconditional support. I can't help but think how different my life would be without your big dreams for me—constantly being told that I had to aim higher made me believe it. I would also like to thank my not-so-little brother, Akhil, for stepping up to the plate these last few years and taking care of the little and big things that slipped through the cracks. Although I don't always say it, I love you all.

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1 Introduction

One of Amgen's core values is "Ensure Quality." The degree to which Amgen internalizes this value is fascinating—"quality-mindedness [1]" is pervasive within all levels of the organizations. As Amgen gears up to introduce an array of patient friendly delivery platforms, Amgen must adjust to a changing regulatory environment while maintaining the highest standard of product quality. There is a great scope for achieving high quality levels through the application of statistical process controls. Although the importance of quality is clear at every level of Amgen, a coherent statistical process control approach is not widely implemented within the clinical organization.

Amgen is currently engaged in rolling out new types of drug delivery platforms, known as combination products. These combination products require new manufacturing processes, assembly processes, and ultimately new quality processes. As Amgen adapts to new combination product regulations, Amgen must also implement appropriate quality processes to support combination product production. These quality processes range from high level business procedures (often termed "big Q Quality") to specialized procedures pertaining to product quality (termed "little q quality").

1.1 General Problem Description

This thesis describes the implementation of process controls to a new final assembly process in the clinical production environment. The primary hypothesis that this thesis strives to substantiate is as follows:

> *Judicious collection and analysis of process data can be a solid basis for assessing current process health, predicting future process health, and improving process quality.*

This thesis will discuss implementation of a control plan, including: the data collection system, methods of data analysis, and results and conclusions. This thesis also attempts to address the fine line between excessive quality investment, and effective quality investment, in addition to the creation of a coherent statistical process control strategy within Amgen's clinical organization. It is important to distinguish that

this thesis particularly focuses on statistical process control techniques within Amgen's clinical production organization—a distinctly separate entity with separate procedural requirements from the commercial production organization.

1.2 General Approach and Results

A control plan was created based on appropriate risk inputs, observational data, and batch release requirements. This control plan was ultimately implemented and a data collection system has been put in place. A baseline set of data forms a cohesive platform for setting control limits across the various control points that are monitored. Ultimately, the work of this thesis is foundational for a continuing quality control cycle. As the process matures, it is intended for the process to evolve. It is also intended for this quality control effort to serve as a flagship for inspiring further such efforts within Amgen's clinical manufacturing organization.

1.3 Thesis Organization

Chapter 1 contains a broad overview of the thesis and its organization.

Chapter 2 contains a background of Amgen and the clinical production group, the FDA's involvement in regulation, and the definition and intent of combination products.

Chapter 3 describes the current state of process control within Amgen and the background and details of the Identify, Track, and Control Variation (ITCV) process control program.

Chapter 4 is a literature review discussion accepted control methods for attribute and variable data, in addition to managerial issues accompanying new process control implementations.

Chapter 5 describes the ITCV implementation, including control point formulation, data analysis, and requirements for long term sustainment.

Chapter 6 discusses recommendations and future work in order to make the ITCV implementation more robust and enduring.

2 Background and Industry

Amgen is a major biologics manufacturer headquartered in Thousand Oaks, California. A large portion of Amgen's organization is dedicated to research and development—however, the focus of this thesis is on the clinical manufacturing organization in Thousand Oaks and its effort to scale up clinical production of autoinjectors, a type of combination product.

As mentioned initially, product quality is a major focus at all levels of Amgen's organization. All employees understand that poor product quality directly affects the lives of patients and caregivers, and thus quality rules the day. This characteristic of "quality-mindedness" is a state that many other organizations struggle to achieve. Juran states:

> *"The principle force for securing compliance with the specifications lies not in the gages, instructions, or other facilities for inspection. It lies in the state of mind of the plant personnel, from the top executives down to the man at the machine...Lacking a state of quality-mindedness among the personnel, no amount of investment in measuring devices and facilities can attain satisfactory control [1]."*

This makes Amgen's clinical organization a particularly fertile environment for implementing quality control measures, as everyone from management to floor staff is eager to cooperate and further bolster product quality. As Amgen's clinical organization ramps up production of combination products, new statistical tools are required to enable quality control of new types of processes.

2.1 Combination Products

The term *biologics* is a portmanteau for *biological products*—a term defined by the United States Food and Drug Administration (FDA) as "any virus, therapeutic serum, toxin, antitoxin, or analogous product

applicable to the prevention, treatment or cure of diseases or injuries of man...[2]" Essentially, biologics are molecules produced by biological processes and are generally significantly more massive and complex than pharmaceutical products produced through chemical synthesis.

Traditionally, biologics are packaged into vials or syringes and administered to the patient by a doctor, nurse, or other healthcare provider in a controlled setting. However, this medium is not always convenient for a patient. A cancer patient receiving biologics often needs to drive to a hospital or clinic to receive his dosage of a cancer biologic after chemotherapy—a daunting proposition when the patient is at his weakest. Increasingly, the biologics industry is turning to alternative drug delivery methods to increase patient ease and quality of life. Amgen, along with other industry players, is engaged in an effort to integrate biologics into medical devices to enable a final product that is more patient friendly. Amgen is coming to realize that these specialized delivery platforms can be a significant business driver:

> *"Our products' competitive position among other biological and pharmaceutical products may be based on, among other things, safety, efficacy, reliability, availability,* ***patient convenience/delivery devices****, price, reimbursement and patent position and expirations [3]."*

These hybrids of medical delivery devices and biologic products are known as *combination products*. Combination products are broadly defined by the FDA to be any combination of drug, devices, and biologics in a single product embodiment [4]. These subparts of a combination product are known as *constituent parts* of a combination product, and have distinct regulatory identities in the eyes of the FDA. Combination products present a unique challenge for biologics manufacturers such as Amgen—with quality systems geared to produce drug products with high precision, physical manufacturing processes and physical components lie outside current quality practices in the clinical organization.

2.2 FDA Regulatory Requirements

The FDA is broadly divided into various centers and offices, of which the Center for Biologics Evaluation and Research (CEBR), Center for Devices and Radiological Health (CDRH), and Center for Drug Evaluation and Research (CDER) are the most relevant to this thesis. Title 21 of the Code of Federal Regulations governs all arenas in which the FDA has oversight. Medical device manufacturer are regulated by Part 820 Quality System Regulation (QSR), which is structured more generally in the style of International Organization for Standardization (ISO) quality systems. Pharmaceutical and biologics manufacturers are regulated by Part 210/211 Current Good Manufacturing Practice (cGMP).

Although the QSR and cGMP quality systems overlap extensively, there are specific areas of variance due to the differences between drugs and medical devices. In January 2013, the FDA issued the final guidance regarding combination product cGMPs which becomes effective in July 2013. This new guidance reflects the changing landscape of combination product regulations. Currently, regulatory jurisdiction is established based on the constituent parts of the combination product. A draft guidance published in 2004 indicates that combination products will be primarily regulated by the constituent part that enables the products primary mode of action. For biologics manufacturers such as Amgen, this generally means that no massive quality system overhauls are necessary as long as the primary mode of action of the combination product is within keeping with the current quality system. However, combination product manufacturers are required to adhere to the quality regulations that are relevant to each constituent part. In the case of Amgen's combination products, this indicates that the biologics constituent part continues to be regulated by the cGMP system currently in place, and that the device components should be regulated by QSR principles [5]. The table provided in the FDA combination product guidance in Figure 1 below indicates the areas a manufacturer following either cGMP or QSR should consider adding as supplements to the current quality system. Amgen is currently working to ensure that these QSR combination product principles are built into Amgen's business processes.

Table 1: Key Current Good Manufacturing Practice Provisions to Consider During and After Joining Together Co-packaged and Single-Entity Combination Products

If the Operating Manufacturing Control System is Part 820 (QS Regulation)		If the Operating Manufacturing Control System is Part 210/211 (CGMP Regulation)	
Carefully Consider These Specific CGMP Requirements	**Title**	**Carefully Consider These Specific QS Requirements**	**Title**
§ 211.84	Testing and approval or rejection of components, drug product containers, and closures	§ 820.30	Design controls
§ 211.103	Calculation of yield	§ 820.50	Purchasing controls
§ 211.137	Expiration dating	§ 820.100	Corrective and preventative actions
§ 211.165	Testing and release for distribution		
§ 211.166	Stability testing		
§ 211.167	Special testing requirements		
§ 211.170	Reserve samples		
* Including all subsections, as appropriate.			

Figure 1. Regulatory guidance for combination product manufacturers

Ultimately, combination product manufacturers must adapt their current quality systems to expand to meet the regulatory needs of combination products. This is especially important for manufacturers who primarily produce only one constituent part—the additional constituent parts of the combination product are not typically core competencies and require further scrutiny.

Both systems largely employ similar terminology that will be used throughout this thesis:

- *Nonconformance* – Any instance where a product or process does not conform to its specifications
- *Corrective and Preventative Action (CAPA)* – Generally formulated in response to a nonconformance. This is a concerted action to correct a causal factor of a nonconformance.

2.3 Product Lifecycle

Biologics-Device combination products follow a different lifecycle pathway from either a biologic or a device alone. As a primary biologics manufacturer, Amgen faces challenges in aligning project management business processes to integrate device development teams and drug development teams.

According to QSR, devices typically undergo design controls during the development phase. These design controls consist of a number of reviews, gating items, and checkpoints to ensure risk management and quality management is inherent in the design from the onset of development. Device development timelines are generally significantly shorter than drug development timelines, which can require that a biologics manufacturer develop specific internal organizational processes to align workflow.

The generic launch pathway followed at Amgen is as follows in Figure 2:

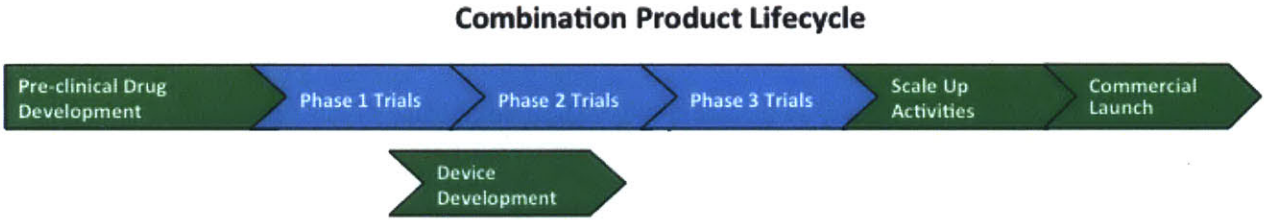

Figure 2. Process description of combination product launch

Pre-clinical Drug Development – These activities include drug discovery and development and generally begin a number of years in advance of device development. Initial pharmacokinetic and pharmacodynamics studies are conducted, in addition to in vitro and animal studies assessing drug viability and safety.

Clinical Trials – Clinical trials are a systematic way of gathering data to support claims for the safety and efficacy of the proposed drug.

Phase 1 Trials – The first stage of clinical trials is aimed at assessing drug safety. A pool of volunteers are drafted, and dosage levels are established. The volunteer pool is usually well below one hundred volunteers.

Phase II Trials – The second stage of clinical trials is intended to evaluate the biological activity or effect on the human body. The trial patient pool is generally larger at around a few hundred volunteers.

Device Development – As a drug is progressing through initial clinical trials with positive results, the need for a device delivery mechanism is assessed as the end patient use scenario is evaluated. Although the exact device development timeline will vary in every scenario, generally development will begin after the intended drug has reached a fairly mature stage of development.

Phase III Trials – The third stage of clinical trials is intended to assess efficacy and safety of the drug on the intended clinical intervention. The pool of volunteers can number up to a few thousand. At this point, it is assessed whether a delivery device should be integrated with the drug, and stability, bioavailability, and human factors considerations are assessed. Based on the new regulatory landscape discussed previously, the FDA has requested that the finished combination products undergo phase III clinical trials, in addition to the drug alone. This is to assess any adverse reactions associated with the combination product as a whole, such as differences in bioavailability. The consequence of this requirement is that the delivery device must be largely production equivalent prior to the clinical trial.

Scale Up Activities – These activities generally include manufacturing scale up, and are ideally timed to coincide with FDA approval of the product.

Commercial Launch – After FDA approval, the combination product can be commercially sold. However, as mandated by both QSR and cGMP, post-launch surveillance must be in place to monitor for adverse events and quality issues. At this point, the product is transferred to commercial manufacturing sites.

2.4 Clinical Production Environment

Amgen is broadly structured into various commercial manufacturing units, and a clinical manufacturing unit based in Thousand Oaks, CA, which supplies clinical trials with product. By necessity, clinical manufacturing must be a flexible organization. Volumes for clinical products are comparatively lower

than commercial products, and are by nature at a lower level of scale-up than commercial products. Namely, products are often produced in small batches, dedicated production lines rarely exist, and changes in formulation must be implemented quickly. Clinical production is a non-revenue generating activity—however, clinical products must adhere to the same high levels of quality as commercial products. These factors often make clinical production a challenging environment for many companies.

The clinical production unit at Amgen operates as a microcosm of the commercial production units with many of the same functional divisions, but at a significantly smaller scale. Upstream teams manufacture drug product and placebo, formulate the dosages, and fill vials or syringes (known as primary containers). The clinical packaging team then labels and packages the primary containers in a *blinded* fashion—such that placebo and true drug product are indistinguishable at the clinical site. Product is then distributed to clinical sites around the world. This thesis will largely focus on the clinical packaging team and their efforts to ramp up autoinjector production.

2.5 Autoinjectors

Autoinjectors are a common type of disposable combination product used to semi-automatically deliver a specific dosage of drug.

Figure 3. Image of an autoinjector [6]

Generally these devices consist of a spring-loaded ejector system and a drug filled syringe. When a trigger is depressed, the spring uncoils and delivers the drug contents. As mentioned before, these

autoinjectors enable patients to administer doses to themselves, instead of taking a trip to their healthcare provider. The basic method of use is shown in Figure 4:

step one: remove the needle cover.

step two: press and hold the DAI™ against the injection site to automatically release the safety interlock.

step three: press and release the activation button to begin delivery. An audible "click" will sound at the start and end of the injection.

Figure 4. Instructions for how to use an autoinjector [6]

Autoinjectors have been most widely used to deliver epinephrine, in the event of anaphylaxis caused by an allergen—these autoinjectors are termed "EpiPens." Previously, stabilizing biologics for potential integration with an autoinjector has presented a challenge. Amgen has overcome this challenge in recent years.

3 Problem Description

This thesis describes the implementation of a process control system on the Amgen clinical autoinjector assembly line. As mentioned before, autoinjector assembly is a new process in the clinical setting, and new quality control processes are required to support this effort.

3.1 The Identify, Track, and Control Variation (ITCV) Program at Amgen

Identify, Track, and Control Variation (ITCV) is an Amgen tool for a method of process control. This program has historically been implemented in various commercial settings in order to address specific quality concerns. As mentioned before commercial statistical process control techniques are different than those used in the clinical setting. For example, ITCV was successfully implemented at Amgen Manufacturing Limited (Puerto Rico) to proactively address trends identified in combination product

complaints. Ideally, ITCV has the potential to ultimately become a quality tool that is implemented as part of a standard quality procedure during process ramp up in both the clinical and commercial production environment. ITCV captures the intent of statistical quality control quite well, illustration the program as a cyclic, evolutionary process. However, ITCV is not broadly implemented within Amgen, and particularly less well known within the clinical manufacturing organization at Amgen Thousand Oaks.

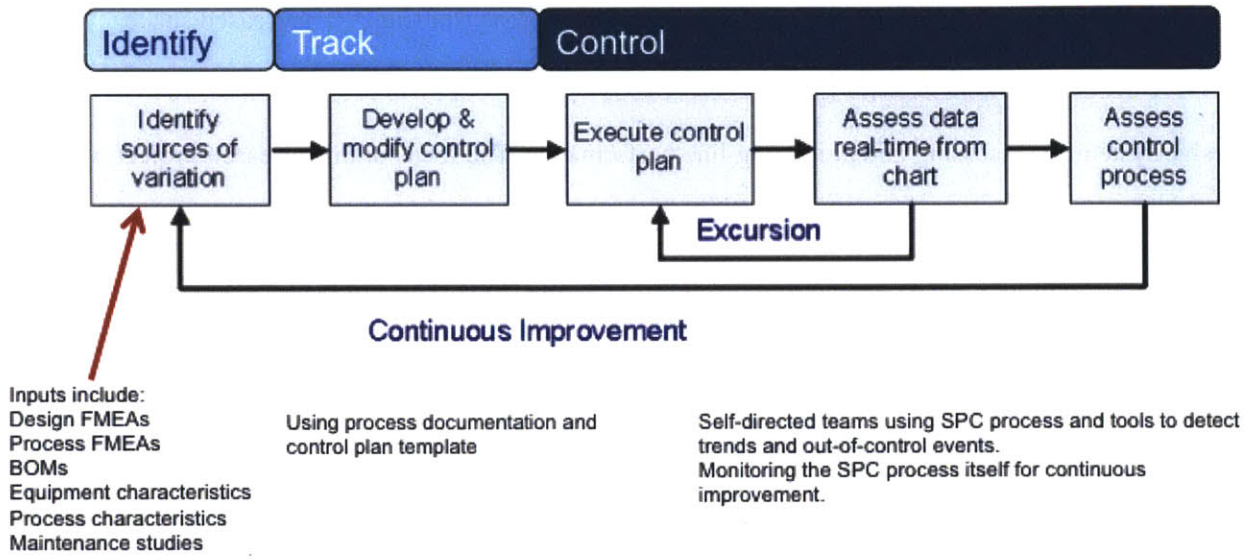

Figure 5. ITCV process diagram

Commercial implementations of ITCV do not necessarily meet the particular requirements for clinical production. Specifically, clinical autoinjector volumes do not merit the use of expensive automation, vision system equipment, and integrated IT systems. As a result, the ITCV program is not currently widely implemented in the clinical packaging space. However, the inherent underlying framework of ITCV, as depicted in Figure 5, is a sound and logical approach for attacking the new challenges that autoinjector assembly brings to the clinical packaging unit. Furthermore, developing ITCV control plans in the clinical setting allows for early identification of important control points when processes are scaled up in the commercial setting. This framework forms the basis for the process control implementation detailed in this thesis.

3.2 Specific Problem Description

Autoinjectors have been built previously on a small scale within the clinical packaging unit, but the new regulations requiring devices to be included in the clinical trial process necessitates production scale-up to significantly higher volumes. Traditionally, the clinical packaging unit has dealt primarily with packaging vials and syringes and labeling these units in a blinded fashion. The introduction of the autoinjector assembly process to the clinical packaging unit presents numerous challenges— increased space requirements, new equipment requirements, increased headcount requirements, and most importantly, a cohesive system for assessing and predicting line performance. The focus of this research project was to implement a control system that could trend historical reject and nonconformance rates, and provide a basis for implementing CAPAs and continuous improvement efforts. This effort was also meant to bolster ITCV visibility as a corporate quality control tool.

3.3 The Case for ITCV implementation

The ramp-up in autoinjector production volumes is a new effort for the clinical production team. The process risk is generally perceived as nontrivial and multiple risk mitigation efforts are being implemented. In the face of this conservative approach, management reception for ITCV implementation was quite positive. Implementation of the ITCV program only increases the data available to make strategic decisions regarding the autoinjector assembly line, and react to negative trends before nonconformances occur.

Ultimately, the body of data and associated learning from the increase production volumes will prove to be a valuable package of information to transfer to the commercial organization upon product launch. The ITCV program is also the first such implementation in the clinical space—lending a distinction to the clinical packaging unit as a leading implementer of continuous improvement processes.

Although the path for ITCV implementation is generally clear, it is important to identify an organizational structure to ensure the program is developed and maintained in an integrated fashion with both the

manufacturing and quality unit processes. Assembly operators must not be distracted with data collection during the assembly process, especially because they are occupied with executing the process. It is crucial to the success of ITCV for a supporting organizational structure to be developed and formalized.

4 Literature Review

Statistical Process Control can be broadly defined as a toolkit of statistical techniques aimed at decreasing variation and increasing quality [7]. Pioneered by Walter Shewhart at Western Electric, a subsidiary of Bell Telephone, process control techniques are as relevant today as they were almost a century ago. Until the early 1930s, most manufacturers were dependent on 100 percent inspection and judgment. In 1924, Western Electric set up an Inspection Engineering Department with the purpose of developing inspection procedures and techniques for controlling fabrication processes. Shewhart was among the personnel assigned to this group and developed the concepts that underlie modern statistical quality control. His concept of the control chart enabled manufacturers to make inferences about process behavior [8]. Ultimately the true power of these control techniques allow manufacturers to not only assess process health, but to make prescient predictions of future process health. The following literature review addresses modern process control techniques used in implementing the ITCV program in the clinical packaging unit.

4.1 Process Control Techniques

In the pursuit of quality control, two options are available to managers: 100% inspection or sampling. 100% inspection is only possible in cases when critical quality attributes can be measured without destroying the product. Furthermore, 100% inspection is often prone to weaknesses such as operator error or test equipment variation [9]. Thus, in many cases it is necessary to engage in a sampling plan. A sampling plan requires random selection a specified subset of product, and assessment of the critical quality attributes of that subset. Thus, the results of the quality tests performed on the subset of product are representative of the entire product batch. Management can then make a decision to accept or reject

the entire product batch based on these results. This thesis will not discuss the methodology for creating and utilizing sampling plans—let it suffice as an assumption for further discussion that a sampling plan is in place. A full discussion of sampling techniques can be found in Ott Chapter 6.

Process control techniques range from simplistic visual plotting techniques to complicated control algorithms. Methods that are most relevant to the processes at hand in this thesis will be discussed. Specifically, since the level of process complexity is quite low and few formal process controls are currently in place, the simplest types of control methods will be reviewed.

Process quality control is considered to have been formally vocalized by Walter Shewhart in the early 20th century. His conviction that "assignable causes of variation may be found and eliminated [10]" led him to formulate the key technique of the control chart—a method for visualizing process performance.

This is a distinct shift from the informal level of process controls utilized in earlier decades, where managers would either improve processes based on experience and intuition or make no attempt towards process improvement at all. The philosophy underlying the formal control chart is to "identify and correct for assignable causes as they occur, and thereby keep variation in the process within its natural limits [11]."

4.2 Process Control Methods for Variable Data

Control charts are one of the most common methods for tracking variation and understanding processes. Although many different forms of control charts exist, control charts are simply a graphical display of a particular quality characteristic with a calculated Upper Control Limit (UCL) and Lower Control Limit (LCL). The graphs provide a useful tool for understanding types of variation and process shifts over time. Additionally, control charts can serve as a visual "scorecard" to operators and managers, and can be useful motivational tools for process improvement.

Variables with associated quantitative data (such as length, hardness, temperature etc.) can be displayed with a control chart, assuming the distribution of the data at hand is normal. Oftentimes, data is collected from product that is sampled from the broader population. Thus, for each batch of product produced, data will be collected from a certain *subgroup.* Common types of control charts are as follows:

4.2.1 Run Chart

A run chart is a very basic control chart—simply a graphical depiction of each single data point in the analysis range (X). A run chart often forms a good basis for beginning to understand a process, although it does not ultimately carry the predictive power of a control chart.

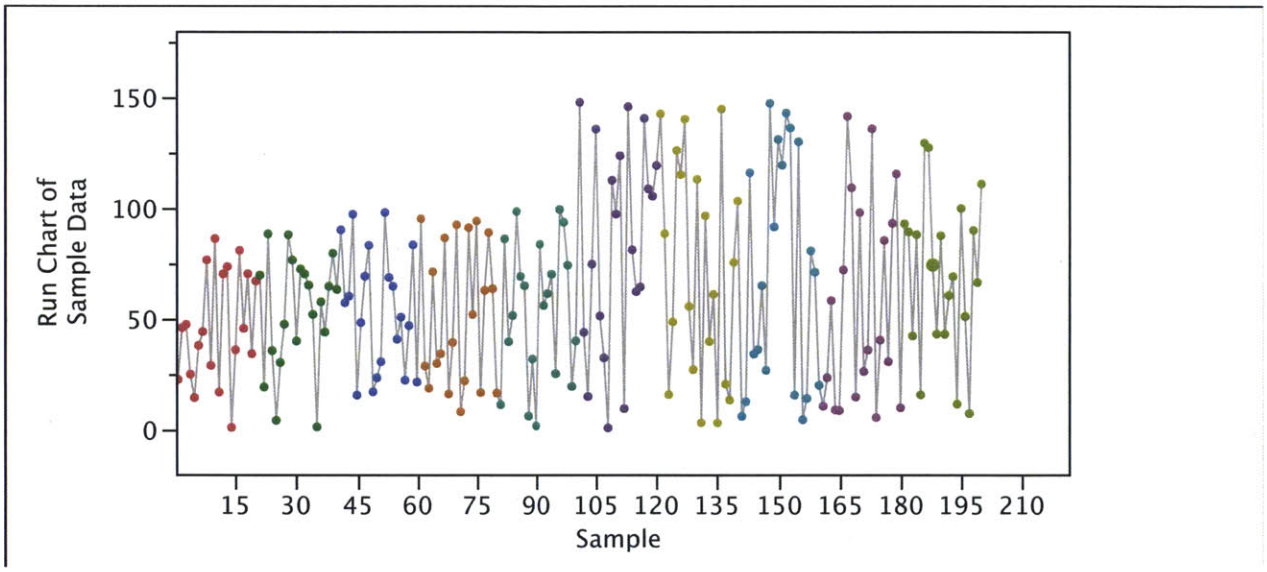

Figure 6. Run Chart of sample data

Figure 6 *above depicts a data set of 200 samples, with subgroup size 20. Even without further analysis, it is clear to see that a greater degree of process variation has been introduced after the 100th sample.*

4.2.2 The $\bar{X}$, *R* Control Chart

$\bar{X}$ refers to the mean of a subgroup. The means of a subgroup are calculated and plotted on an $\bar{X}$ graph. R refers to the range of a subgroup—essentially a measure of dispersion of the data. The range is simply calculated by subtracting the lowest value of a data set from the highest.

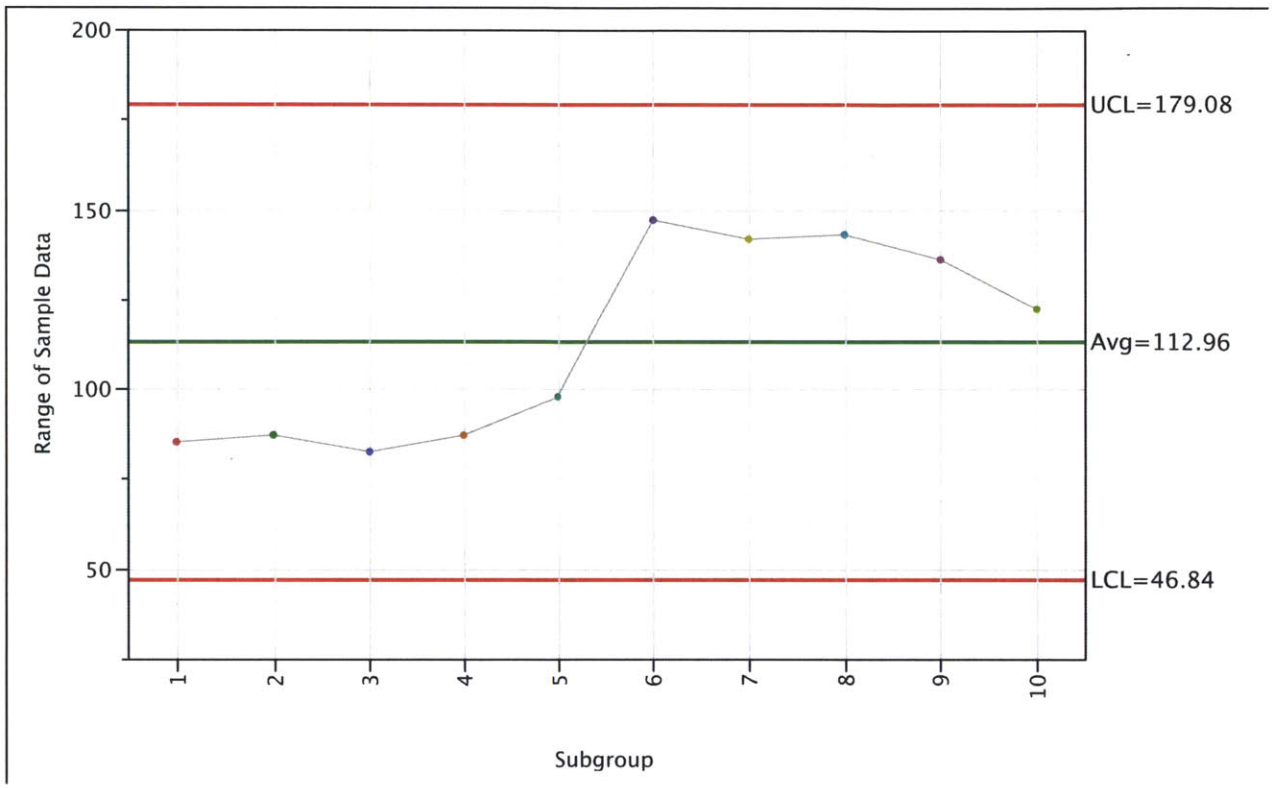

Figure 7. r chart of sample data

The Range of the 10 subgroups displayed in the run chart prior is shown in Figure 7 *above. It is clearly visible that subgroup dispersion in subgroups 6-10 has increased relative to dispersion in subgroups 1-5. In general, R is calculated with the following formula:*

$$R_i = X_{high} - X_{low}$$

The centerline, UCL, and LCL are calculated as follows below (control chart constants are drawn from Appendix A):

$$centerline = \bar{\bar{R}} \qquad UCL_{\bar{R}} = D_4\bar{R} \qquad LCL_{\bar{X}} = D_3\bar{R}$$

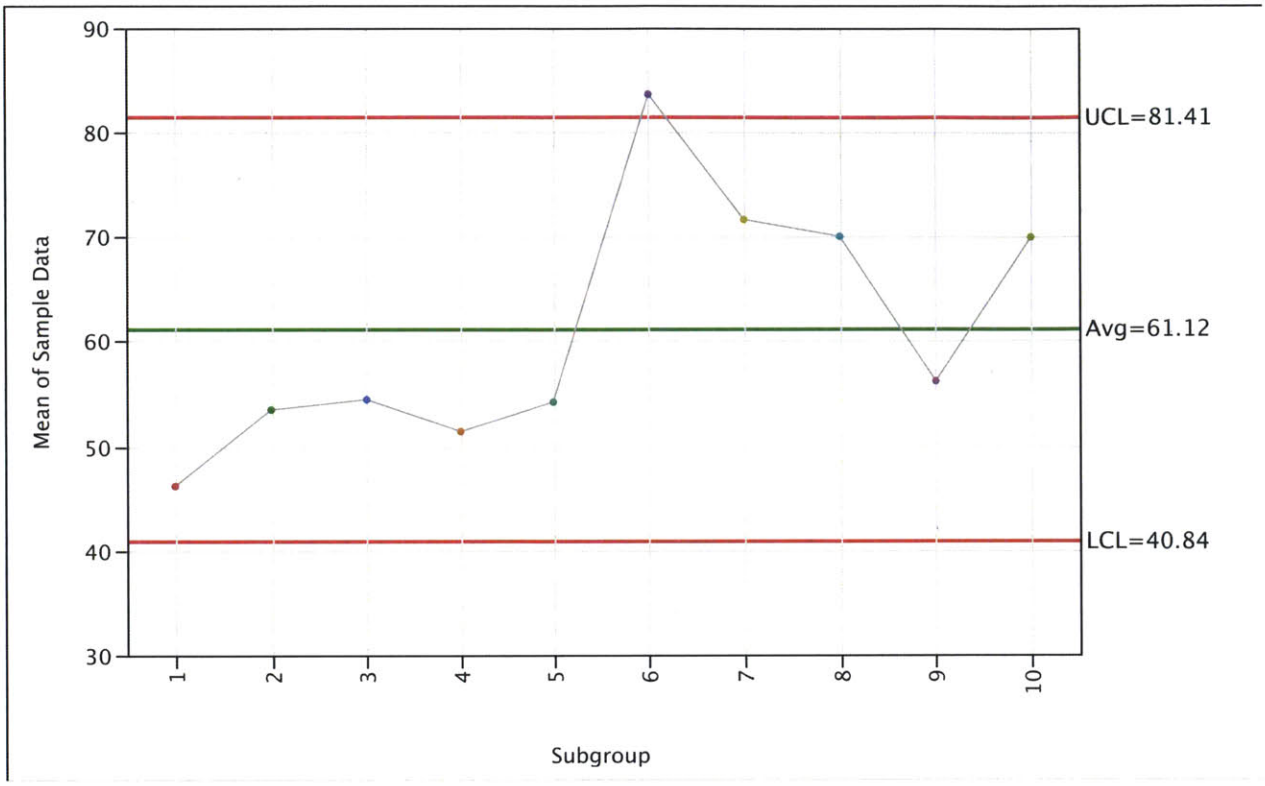

Figure 8. X-bar chart of sample data

The subgroup means of the 10 subgroups displayed in the run chart prior are shown in Figure 8 *above. It can be visually deduced that the means have changed based on the out of control point for subgroup 6. In general, each point is calculated with the following formula where X refers to an individual data point in subgroup i and n is the number or samples in subgroup i:*

$$\bar{X}_i = \frac{\sum X}{n}$$

The centerline, UCL, and LCL are calculated as follows, where n refers to the subgroup size, and sigma is the standard error (control chart constants are drawn from Appendix A):

$$centerline = \bar{\bar{X}} \qquad UCL_{\bar{X}} = \bar{\bar{X}} + A_2\bar{R} \qquad LCL_{\bar{X}} = \bar{\bar{X}} - A_2\bar{R}$$

4.2.3 The $\bar{X}$, s Control Chart

$\bar{X}$, s control charts are quite similar to the X-Bar, R chart discussed above. Instead of plotting R, the standard deviation s is calculated instead. This is valuable when subgroup sizes are relatively large (n>10) or when the sample size is variable. Furthermore, the s statistic becomes simple to calculate when computers are available to perform the computation.

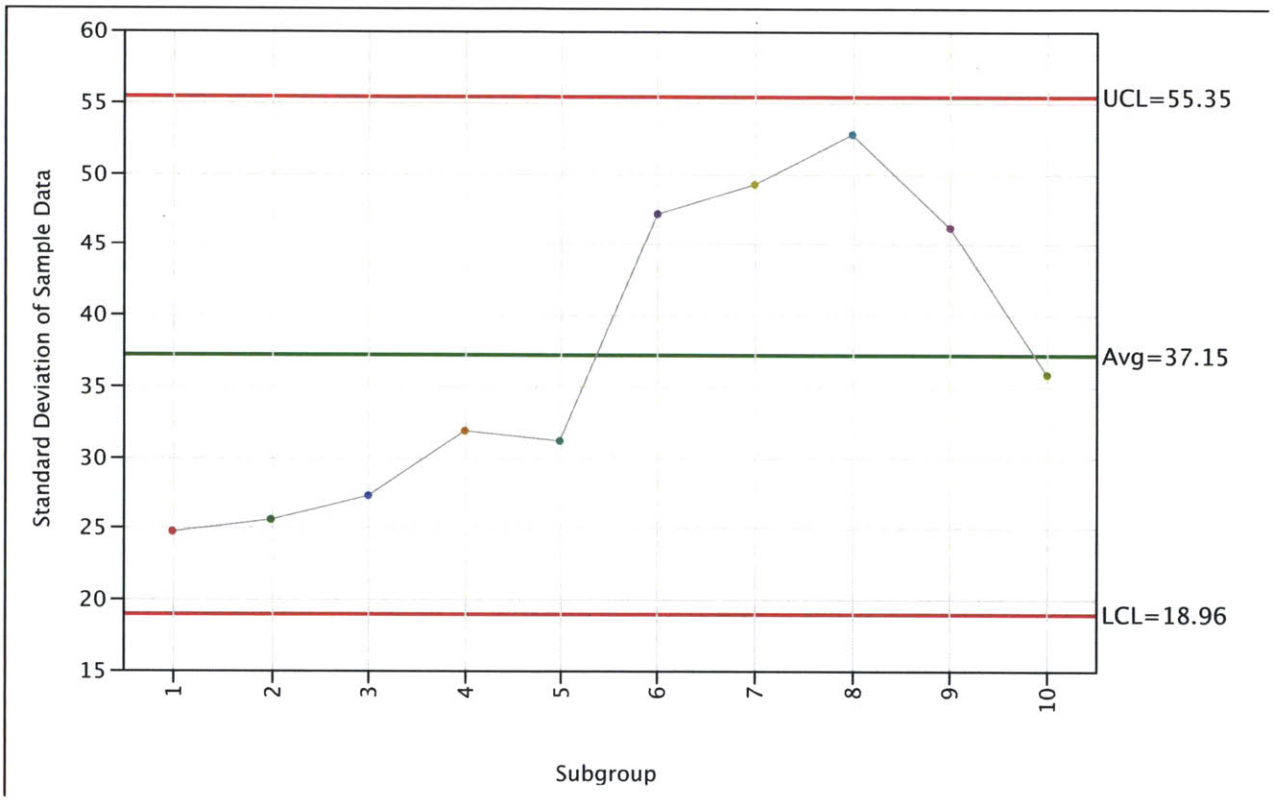

Figure 9. s chart of sample data

The same data set in the previous example is displayed as a standard deviation chart in Figure 9. *Note that the UCL and LCL are significantly tighter, and that the trend is more pronounced. The standard deviation s is calculated as follows:*

$$s = \sqrt{\frac{\sum_{i=1}^{n}(x_i - \bar{x})^2}{n-1}}$$

The centerline, UCL, and LCL are calculated as follows (control chart constants are drawn from Appendix A):

$$centerline = \bar{\bar{s}} \qquad UCL_{\bar{X}} = B_4\bar{s} \qquad LCL_{\bar{X}} = B_3\bar{s}$$

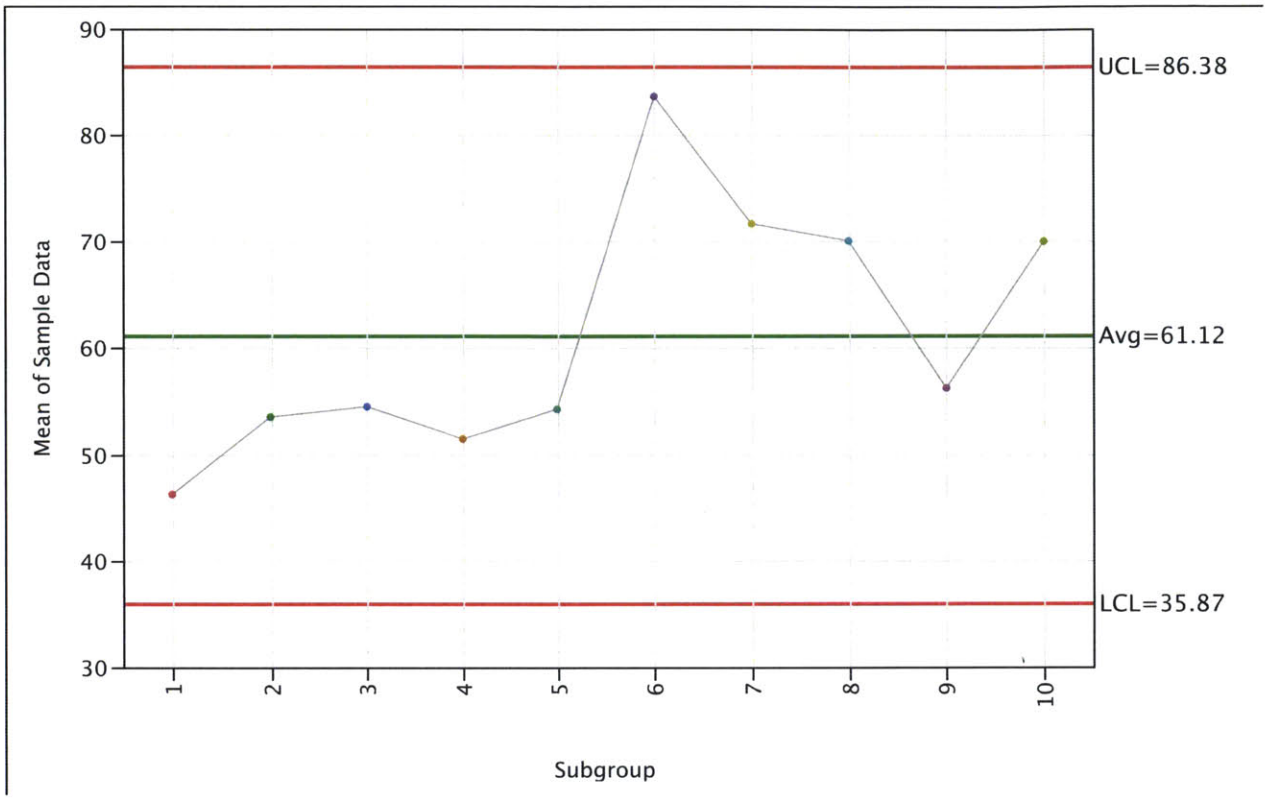

Figure 10. X-bar chart of sample data

Again, the same data set from the previous example is plotted. Note the slight differences in UCL and LCL. Also note that subgroup 6 is no longer outside the control limits. With this type of analysis, it appears that the process is still within controls. Although this data is purely fictional, this serves to highlight the importance of choosing the appropriate type of control chart and control chart parameters. $\bar{X}$ *is calculated in the same fashion as explained in the previous section. However, the centerline, UCL, and LCL are as follows (control chart constants are drawn from Appendix A):*

$$centerline = \bar{\bar{X}} \qquad UCL_{\bar{X}} = \bar{\bar{X}} + A_3\bar{s} \qquad LCL_{\bar{X}} = \bar{\bar{X}} - A_3\bar{s}$$

4.3 Process Control Methods for Attribute Data

It is sometimes convenient to collect attribute data in place of variable data. Attribute data usually takes the form of reject rates and nonconformance proportions. Essentially, this is a binary notation of whether a particular issue was found or not. Since there is no numerical measurement associated with attribute data, a typical control chart cannot be used to provide meaningful data. However, various control charts exist that allow for plotting attribute data.

4.3.1 The *p* Chart

This chart exerts control based on the proportion of defective units per batch. Control limits can then be calculated for proportion defective. The p chart is also a good visual depiction of overall quality, as it can give an indication of overall defects for a process. One drawback to the p chart is that no information on the *types* of defects is included. A pareto chart, to be discussed below, is necessary to provide further insight into the sources of variation an defects.

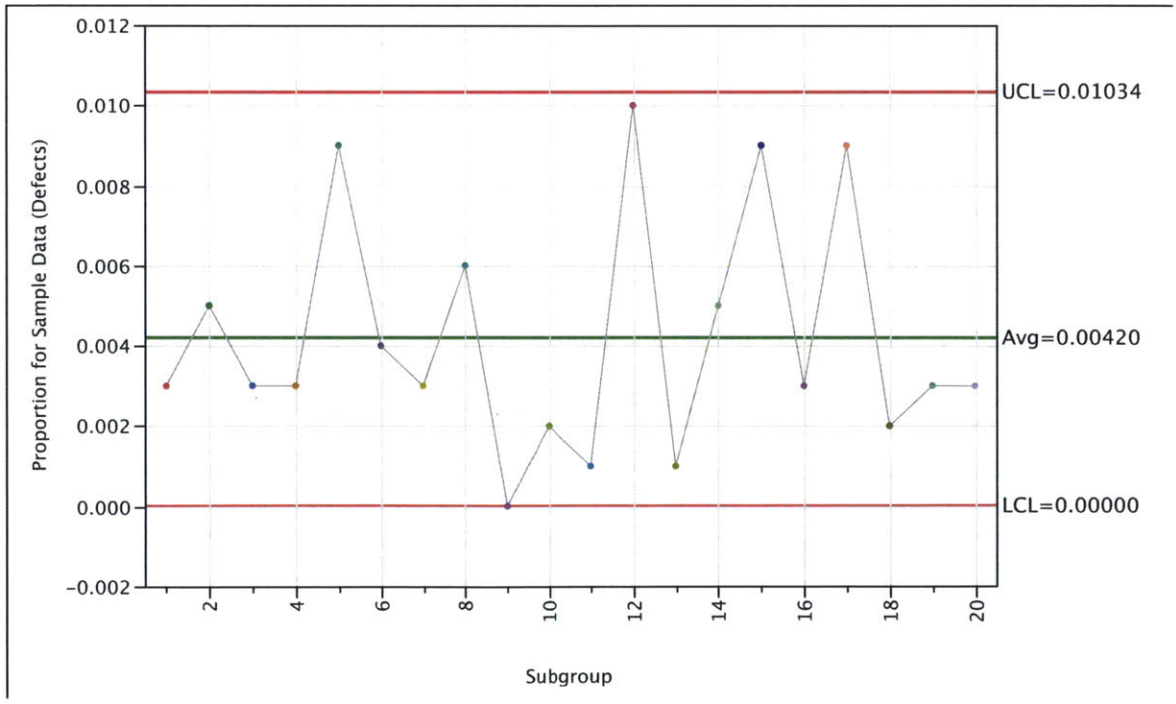

Figure 11. p chart of sample data

The p chart depicted in Figure 11 *consists of sample data, and depicts a process that appears to be in control. The p statistic is calculated as follows, where np is the number of defects within a sample, and n is the sample size:*

$$p = \frac{np}{n}$$

The centerline, UCL, and LCL are calculated as follows:

$$centerline = \bar{\bar{p}} \qquad UCL_{\bar{p}} = \bar{p} + 3\sqrt{\frac{\bar{p}(1-\bar{p})}{n}} \qquad LCL_{\bar{p}} = \bar{p} - 3\sqrt{\frac{\bar{p}(1-\bar{p})}{n}}$$

4.3.2 The Pareto Chart

Named after Vilfredo Pareto (1848-1923), the pareto analysis was originally used to study the distribution of wealth in Italy. Pareto found that 80 percent of the wealth belonged to 20 percent of the population. This, in addition to various studies performed over the years in other fields, gave rise to the "80/20" rule, where 20 percent of inputs are correlated with 80 percent of the outputs [12]. Juran applied this principle to quality to distinguish between the "vital few" and "trivial many [12]." A pareto analysis is used today in quality analyses to understand the frequency of various issues contributing to nonconformances.

A pareto chart is constructed by assembling a cumulative distribution of the causes of variation, and is often paired with a bar graph of the causes. An example is as follows [13]:

Given the following data regarding operators and defect counts:

	Operator	Count
1	A	4
2	B	10
3	C	0
4	D	22
5	E	2
6	F	8
7	G	4

We can reorder the operators from high to low, and calculate what percent of total defects each individual is responsible for. A cumulative percentage is also recorded.

	Operator	Count	%	Cumulative %
4	D	22	44%	44%
2	B	10	20%	64%
6	F	8	16%	80%
1	A	4	8%	88%
7	G	4	8%	96%
5	E	2	4%	100%
3	C	0	0%	100%
Total		50	100%	

The results are graphed below:

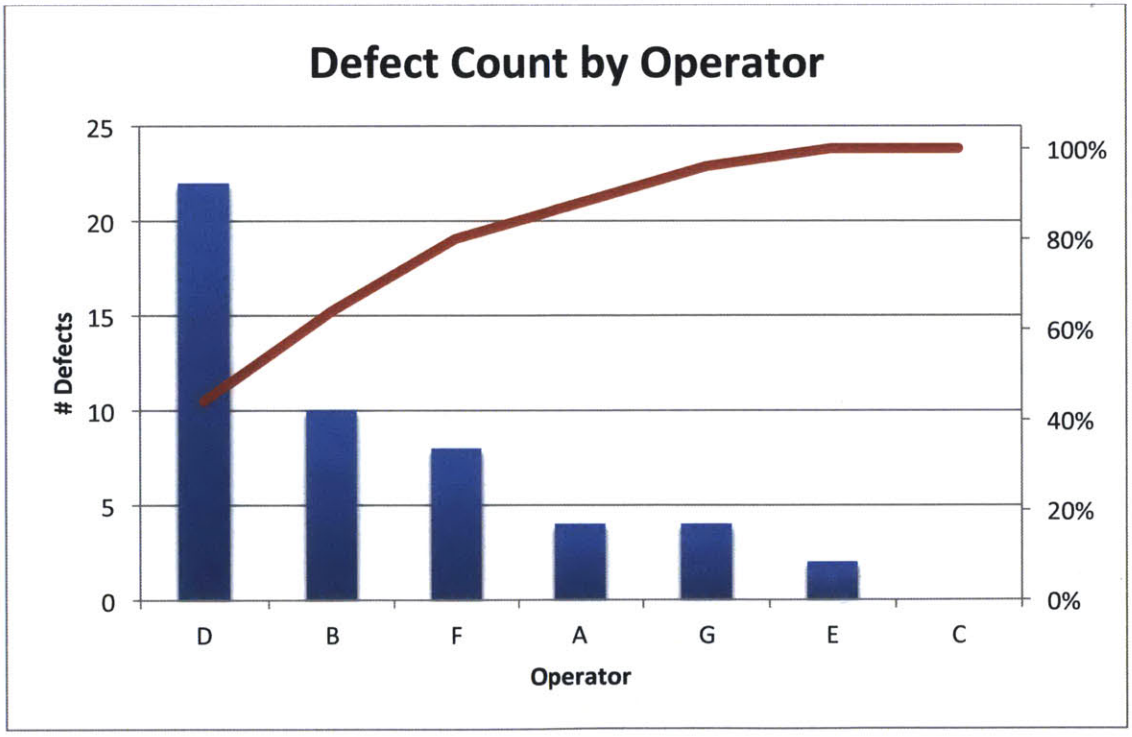

Figure 12. Pareto chart analysis of sample data

Although the example is simplistic, the pareto chart in Figure 12 clearly illustrates that operator D causes significantly more issues than the other operators. This method is a simple way of highlighting causal factors.

4.4 Implementation of Quality Control Procedures in Organizations

Various challenges can arise when attempting to implement new quality control procedures in an organization.

4.4.1 Resistance to Change

The introduction of any new procedure or policy invariably encounters resistance in an organization, largely due to social or cultural reasons. Disruption of the cultural pattern within an organization is often difficult to avoid when implementing new process control techniques. Juran offers an enlightening checklist of advice to the process control champion:

1. *"Secure the active participation of those who will be affected during both the planning and the execution of the change.*
2. *Strip off all the technical cultural baggage not strictly needed for introducing the change. (Many quality control engineers have been in violation of this.)*
3. *Reduce the impact of the changes by weaving them into an existing broader pattern of behavior, or by letting them ride in on the back of some acceptable change.*
4. *Put yourself in the other fellow's place.*
5. *Make use of the wide variety of methods available for dealing with resistance to change.*
6. *Treat people with dignity [14]."*

This checklist, although formulated in the 1960s, is still largely relevant for organizations today.

4.4.2 Employee Evaluation

Control charts are useful because they provide a metric for evaluating a process. However, control charts not only reflect performance of a process, but can represent the underlying performance of the floor operator. Different scenarios can ensue:

- It may be useful for an organization to track individual operator performance. This can be used as an input to setting compensation or evaluating for promotion. This data can provide the hard facts to ensure that employee compensation is fair and transparent [15].
- Using control charts as a report card can also have a deleterious effect on employee morale. If a statistical system is in place for tracking individual performance, but is not used for personnel decisions or is used incorrectly, "everybody will suppose that there are good reasons for the selection and will be trying to explain and reduce differences between people [15]."
- Even if a control chart for tracking individual performance is in place and is appropriately used, such a system can destroy employee fraternity. If employees are competing against each other, the environment of teamwork is lost, and can have negative results on overall morale [15].

Thus, it is important to utilize such systems for tracking operator performance wisely, and ensure that morale remains high.

4.4.3 Qualified Personnel

It is important to ensure that qualified personnel are associated with implementing process control change. A combination of a basic understanding of statistical terminology, familiarity with local business processes, and quality methods is required to effectively implement new process control strategies. Ultimately, it is necessary that the organization source effective personnel to ensure that the quality effort succeeds.

5 Clinical Process Control Implementation

5.1 Process Description

In the final implementation of the auto injector assembly line, the process flow is as follows in Figure 13:

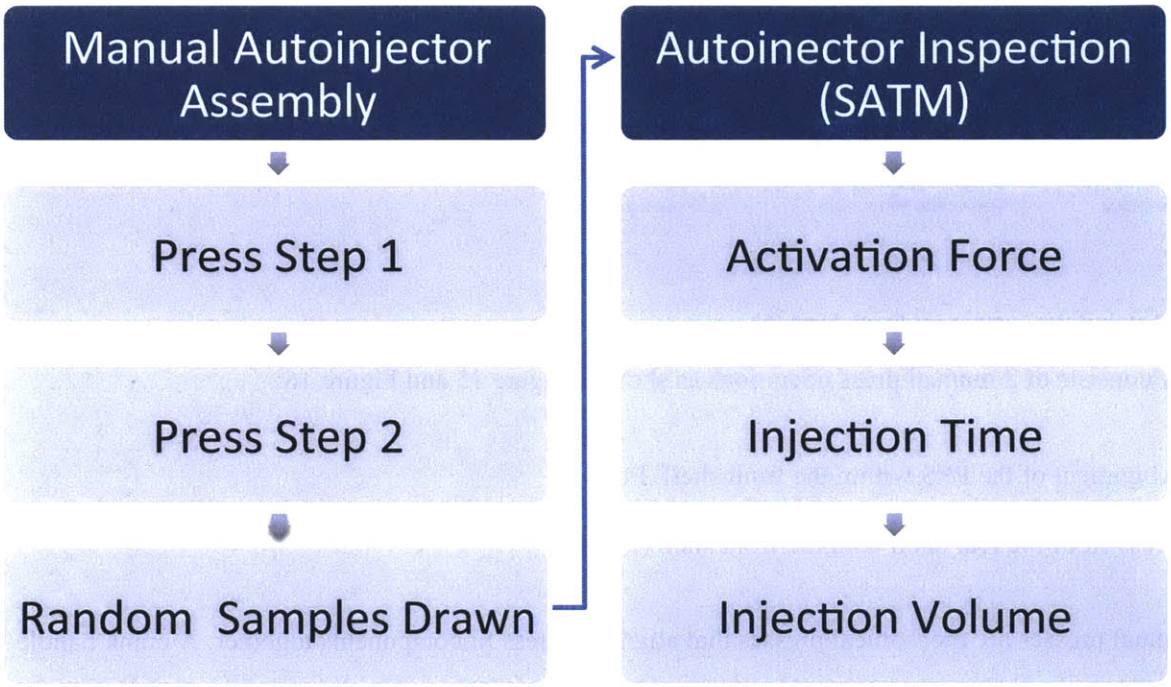

Figure 13. Process flow diagram of autoinjector assembly and inspection process

Autoinjectors consist of three main components as shown in Figure 14:

- Pre-filled syringe (PFS) containing a predetermined dosage of drug
- Rear shell containing spring-loaded ejector system and button trigger
- Front shell containing removable needle guard and clear window to confirm injection of the full dosage

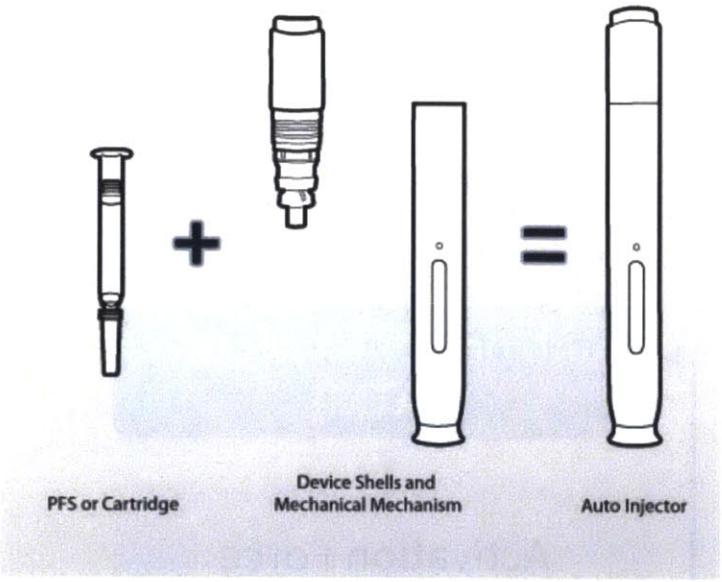

Figure 14. Autoinjector component breakdown [6]

Assembly consists of 2 manual press operations as show in Figure 15 and Figure 16:

- Alignment of the PFS within the front shell (Press 1)
- Press fit of the rear shell with the front shell (Press 2)

These manual presses are mechanical presses that align and press fit components together. A crank handle serves to activate the main head of the press downwards.

Figure 15. Assembly press 1

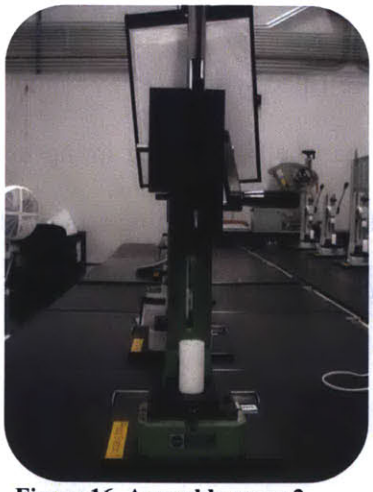

Figure 16. Assembly press 2

These units are then sampled and destructively tested on the Semi-Automatic Testing Machine (SATM) as depicted in Figure 17 and Figure 18. The SATM activates the autoinjector trigger and records activation force, injection time, and injection volume. These three variables are not measured separately—instead they are measured from a single test sequence when the product is activated. Each batch is analyzed for excursions, and if an excursion is found, a nonconformance is logged and the batch is quarantined for further review.

Figure 17. Semi-Automatic Test Machine

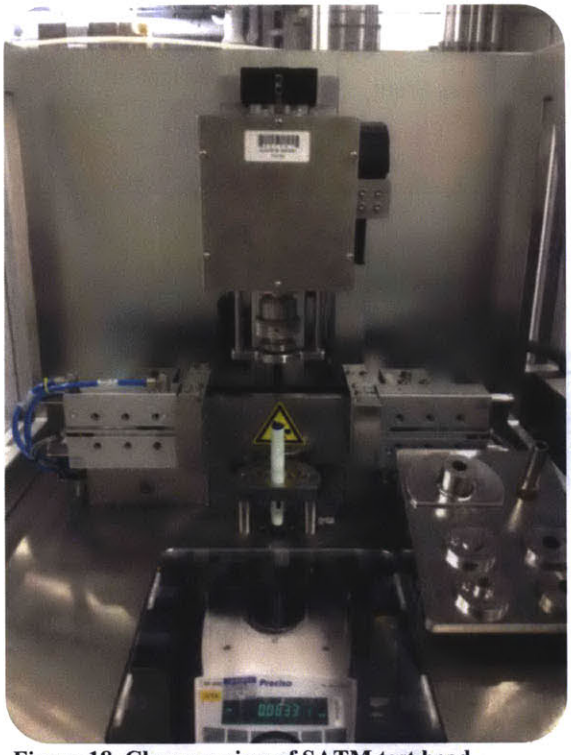

Figure 18. Close-up view of SATM test head

5.2 Process Risk Analysis

The control plan has been initially formulated based on a Process Failure Mode and Effects Analysis (FMEA) conducted by a cross functional team. Specific representative samples of the PFMEA are show below in Figure 19. Scoring is omitted.

Component / Section / Function / Requirement	Potential Failure Modes	Potential Effects of Failures	Potential Cause
Manual Press Front Assembly	Misalignment of syringe on the press	Broken syringe (Gross breakage)– CCI Infection	Human Error
Manual Press Front Assembly	Misalignment of syringe on the press	Broken syringe (visible cracks)– CCI Infection	Human Error
Autoinjector testing in the SATM (Syringe Automated Testing Machine)	Failure to test the samples	Production delay – reconciliation issues.	Human error
SATM Test for injection time and volume (Module C)	False Pass	Painful injection	Equipment failure - incorrect injection time parameters – injection time too long – software defect

Figure 19. Table of selected PFMEA examples

These Failure Modes are a sample of the level of granularity of the PFMEA. This in-depth review highlights that the major concerns of the cross-functional team include human error and SATM malfunction. These are major inputs to the control plan.

5.3 Control Point Formulation

The PFMEA discussed above forms the cornerstone for control point formulation. The majority of failure modes identified in the PFMEA have the associated cause of "operator error." As a largely manual process, this is natural. As a result, the control plan focuses largely on areas of operator error.

Autoinjectors also have batch release characteristics that are required to be measured before a lot can be released. These requirements included the SATM test parameters of injection time and deliverable volume. As mentioned earlier, the SATM collects injection time, deliverable volume, and activation force data during the same test sequence—thus activation force is also collected and analyzed despite being a less important characteristic than injection time and deliverable volume.

The final control points are formulated based on initial assembly run data. During assembly of the first batch, it became apparent that there were rejects that could not be categorized into any of the pre-formulated categories. Thus, new categories were added to accommodate for new types of rejects.

The complete control chart is presented in Appendix B and includes control limits and control activities. The various control points are discussed below in Figure 20. Note that a particular rejected unit can be associated with multiple control points. For example, an autoinjector that was dropped and resulted in breakage of the syringe would be categorized with "Improper Handling" and "Glass Breakage." Type denotes the type of characteristic, attribute or variable, as discussed before.

Control Point	Location	Type	Description
Gross Autoinjector Defects	Assembly Area	Attribute	Any visible defect including, but not limited to: chips, scratches, cracks, and discolorations.
Glass Breakage	Assembly Area	Attribute	Units with observed glass breakage.
Abnormal Sensation During Press Stroke	Assembly Area	Attribute	Units where the appropriate proprioceptive feel was not observed during press stroke. This was an observed issue in initial runs, and was retroactively added to the control plan.
Improper Handling	Assembly Area	Attribute	Any units dropped to the floor, and any units with inserted syringe that are dropped to the floor or table.
Misalignment During Assembly (Rear)	Assembly Area	Attribute	Misalignment is observed during first press step.
Misalignment During Assembly (Front)	Assembly Area	Attribute	Misalignment is observed during second press step.
Syringe Barrel Dimension too Large for Press	Assembly Area	Attribute	Syringe barrel does not fit into nest on first press, and thus press step cannot be completed. This issue was observed repeatedly in an isolated batch and originally logged as "other." It was then retroactively added to the control plan and formalized as a category.
Other	Assembly Area	Attribute	This is intended to be a "catch-all" category to track issues that are not explicitly assigned a category. When a reject is tagged as other, it is required that a description of the issue be included. When an issue makes multiple appearances, it is formalized as a category.
Activation Force	SATM	Variable	Force (kg) required to depress autoinjector activation button.
Injection Time	SATM	Variable	Time (sec) required for autoinjector injection to complete upon activation.
Deliverable Volume	SATM	Variable	Volume (mL) of drug product delivered by autoinjector.

Figure 20. Table of control points

5.4 Data Collection

Attribute data is collected by floor operators using a specifically developed electronic data collection spreadsheet. When a defect is noticed at a press station, the press operator will raise his hand and give the unit to the floor manager. The floor manager then enters the relevant information into the entry form depicted in Figure 21. The floor users only have access to the entry form, and the submitted data is locked by password to prevent any tampering. Furthermore, constraints are placed on all the data entry fields to ensure the correct type of data is entered—for example, a numerical value must be entered into the batch number field. Additionally, a notes section is available for additional notes.

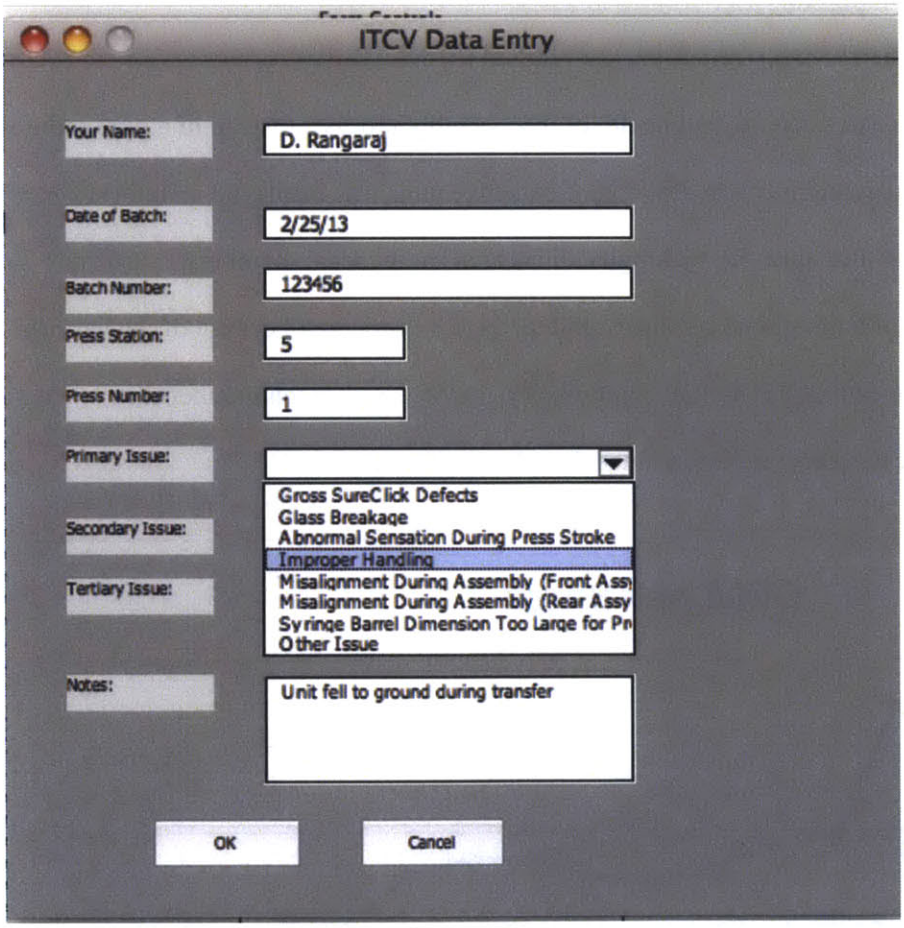

Figure 21. Defect logging entry form

SATM data is not collected by the streamlined process described above. Data is located locally on the machine hard drive, forcing the data collector to physically travel to the machine and export the data. This

process requires a significant amount of time for the analyst, and is a significant constraint of the current process. As volumes rise and more data is generated, it is unreasonable to expect that a significant percentage of personnel time is devoted to data collection. It is hoped that additional IT resources can automate this process in the future and eliminate this constraint.

5.5 Analysis and Trending (Attribute Data)

Due to the nascent nature of the autoinjector assembly process, attribute data was collected on a 100% inspection basis. For each of the attribute quality variables, each press operator was instructed to reject any product that appeared to be nonconforming. Thus, every unit was inspected during assembly.

5.5.1 Overall Process Health

Two similar charts were used to assess the overall health of the assembly process. Instead of a pure ratio as described in section 4.3.1 discussing p charts, fraction of defective units was displayed in defects per million (DPM) because it is a familiar quantity to Amgen clinical packaging team members. Furthermore, the control limits of a traditional p chart would merely be distracting because of the varying autoinjector build sizes (see Appendix C). The first chart displays DPM versus batch number (in chronological order). This indicates general performance from batch to batch.

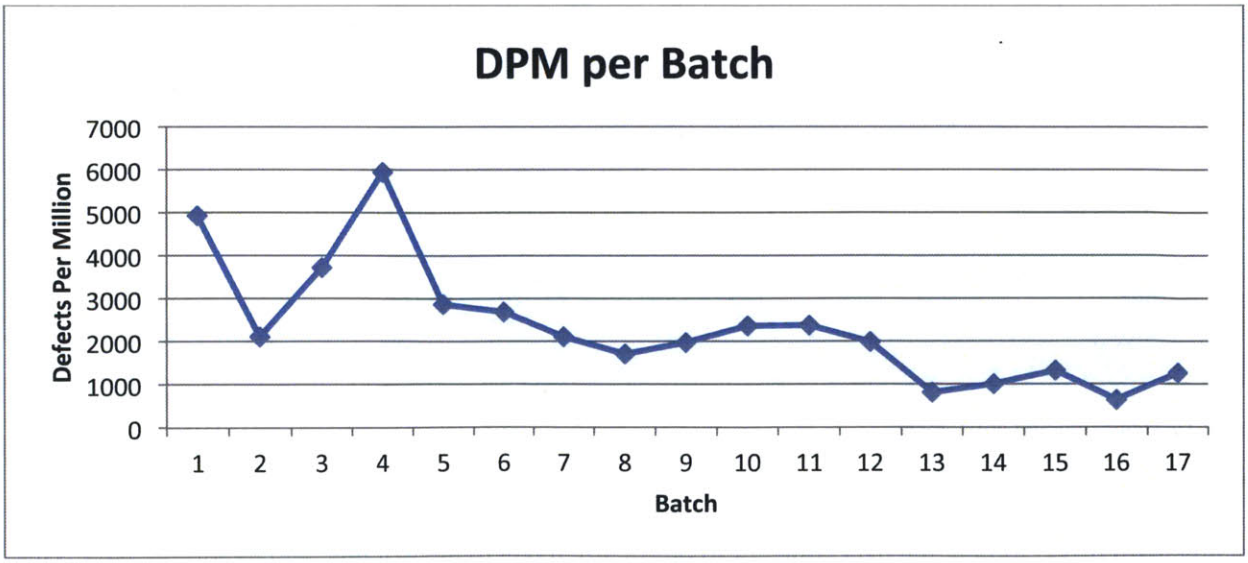

Figure 22. DPM per batch by batch number

Figure 22 clearly illustrates the "learning curve" phenomenon. Initial batches resulted in higher defect rates, and gradually improved to settle into a lower defect level, demonstrating that the organization is gaining economies from repetition. It is important to note that two builds consisting of about 10,000 units in sum were conducted before the ITCV data collection system was implemented, and thus the entire learning curve is not captured.

The next graph to assess overall process health considers the factors of time and batch size. DPM is plotted against the date, and bubble size indicates the relative size of the build.

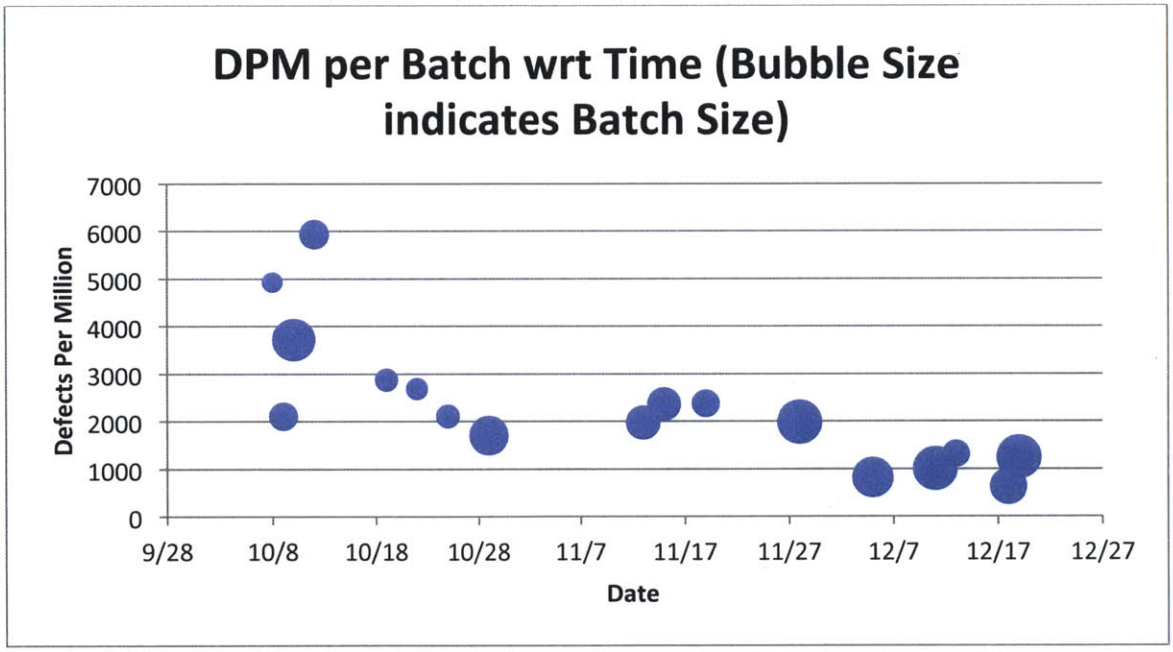

Figure 23. DPM per batch by time. Bubble size indicates batch size.

Figure 23 allows manufacturing personnel to understand whether operator fatigue is contributing to defect rates. It is theorized that operators could potentially experience fatigue if a batch is particularly large or if builds are performed on consecutive days. It is important to note that builds are usually performed over a single day, regardless of batch size. If a batch is small, fewer operators are engaged. If a batch is large, more operators are scheduled and overtime is utilized. However, no significant evidence is visible from the results of this graph to identify the presence of operator fatigue. It is important to monitor this graph

over time, and perhaps perform a more in-depth statistical analysis when a larger data set has accumulated.

5.5.2 Causal Factors Analysis

For each reject logged, information on the operator press station was also collected. From this data, it is possible to perform a pareto analysis analyzing the distribution of press stations where rejects were identified. This allows manufacturing personnel to assess whether a particular press is having mechanical issues. Unfortunately, operators are not currently constrained to sit at the same presses, and the same subset of operators is not always present for a build. Thus, it is not possible to use this information to trace back to a particular operator. A pareto analysis of press stations logged in the months of November and December is shown below. Over 100,000 units were assembled within this time period.

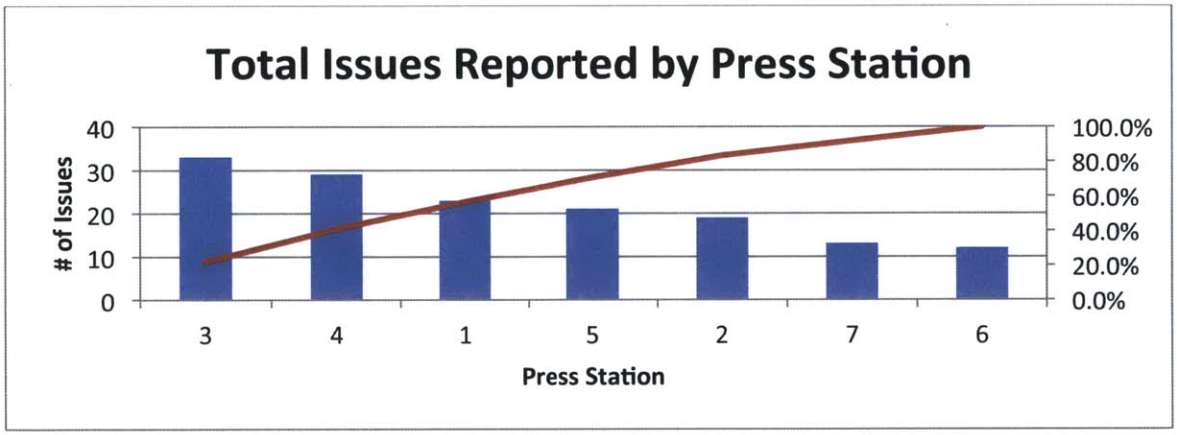

Figure 24. Pareto analysis across press stations

Press stations 6 and 7 are not used when smaller builds are performed, and thus have a noticeably lower issue count. There does not appear to be a striking visible difference between the remaining press stations in Figure 24, however it is important to perform a statistical analysis to confirm this when more data has been collected. Ideally, the granularity of the data collection system could be increased to include a tie to the operator. Some operators may be more zealous in observing and flagging rejects, and some operators may be less adept than others. Any implementation of this kind would need to be done cautiously, so as not to seem like a method for criticizing individual performance.

A pareto analysis of rejects logged in the months of November and December is shown below in Figure 25. Over 100,000 units were assembled within this time period.

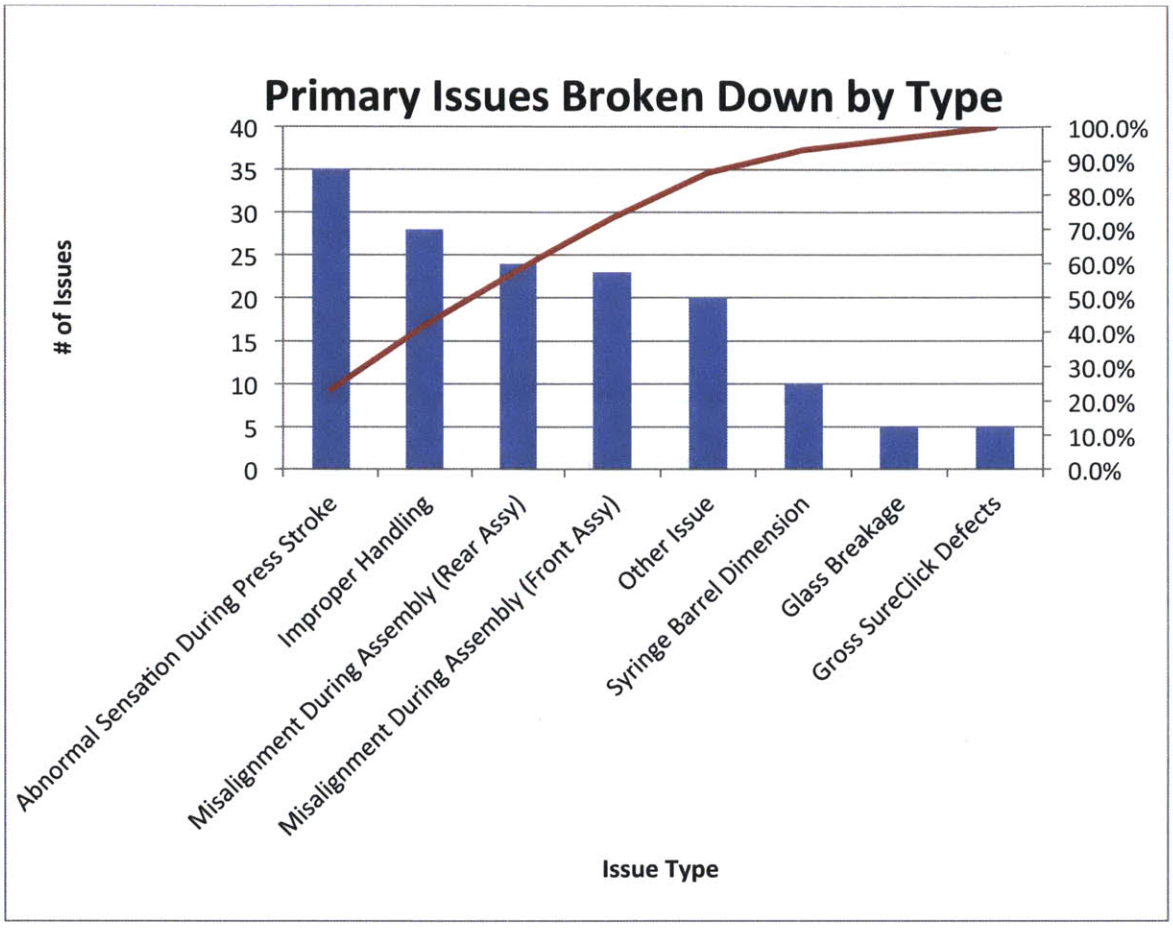

Figure 25. Pareto analysis by issue type

Abnormal sensation, improper handling, and misalignments account for approximately 80% of the issues observed. This leads to interesting recommendations regarding corrective actions.

> *Abnormal sensation during press stroke*—Currently, abnormal sensation units are rejected in order to take the most conservative approach to reject segregation. It is currently unknown whether a deviation from the normal proprioceptive feel of a press stroke indicates the presence of a deviation. Since these units form the greatest fraction of rejected units, it is natural to analyze the failed units to determine whether this ambiguous causal factor truly forms a basis for

rejection. It is recommended that units tagged with the abnormal sensation issue be segregated and tested to determine whether any defect can be observed in appearance or in function.

The other rejection categories do not present a pressing need for analysis or corrective actions at the moment. Although it is ideal for process improvement to advance upon all fronts, rejection categories with constant low levels should be considered as part of the baseline human error for the process. For a relatively small manufacturing environment, diminishing returns are obtained by trying to completely eliminate small sources of error.

Improper Handling—Improper handling can only be reduced with proper operator training and care. However, it is unlikely that improper handling can ever be eliminated due to the manual nature of the process. As long as this causal factor can be controlled and a constant low level, there is no reason to address the issue.

Misalignment—Misalignments appear to occur with roughly similar frequencies in press step 1 and press step 2. This may be due to a combination of operator error, or equipment error. It is recommended that this category be monitored for issues associated with any one press station or operator to ensure that misalignments are not associated with any particular causal factors.

Other—The rejection tag of "other" consists of various rejection scenarios. Until a rejection scenario becomes significant enough to warrant creation of another formal category, these scenarios are tagged as "other" in the data logging system and the operator enters an explanatory note. Scenarios within this data set include:

- Double insertion – operator forgets that he has already aligned syringe within rear assembly at press step 1, and inserts a second syringe. This causes glass breakage and damage.
- Needle cap falls off – when the needle cap is removed from the syringe, the drug product is no longer usable.

- Visible sediment in syringe – when visible sediment is observed within the syringe, the product is not used for cosmetic reasons.
- Autoinjector jumped in nest – operator notices that the autoinjector shifted in the nest during the press stroke. Although this is a soft causal category similar to abnormal sensation, so few units have been tagged with this note that it does not merit immediate attention.

5.6 Analysis and Trending (Variable Data)

The following data is obtained from sampled product subgroups destructively tested on the Semi-Automatic Testing Machine (SATM) discussed above. Each sampled subgroup consists of 49 units, although in the initial test batches, some data was lost due to machine error and differing file naming conventions. Three subgroups are sampled from the beginning, middle, and end of each production batch. An $\bar{X}$, s control chart was chosen as the vehicle of analysis for the quantitative quality variables, because subgroup sizes are large (n>10) and the initial subgroups vary in size due to the aforementioned reasons. Results for the three major tests will be discussed.

5.6.1 Activation Force (ATF)

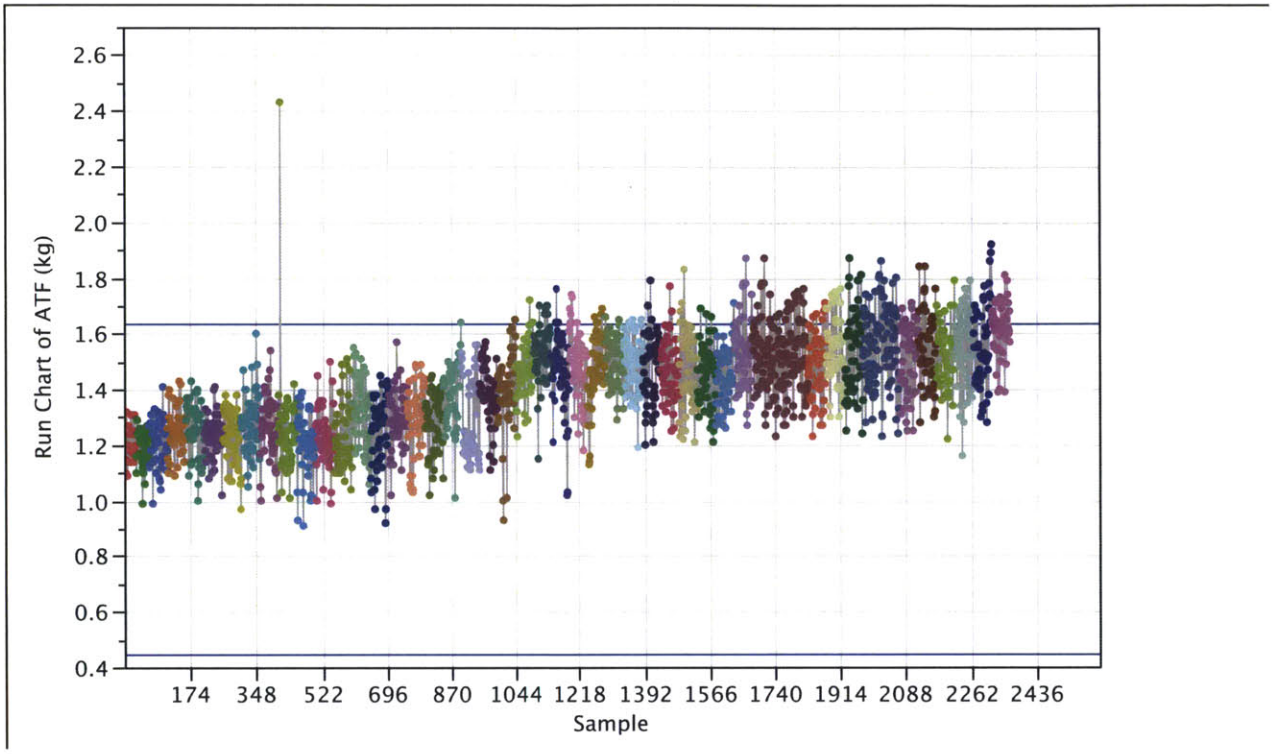

Figure 26. Run chart of ATF

From the run chart in Figure 26, it is easily observable that a process shift has occurred somewhere between sample #522 and sample #1218. It is interesting to note that the shift is gradual—indicating that the reason for the variation did not occur instantaneously. In the following control chart analysis, the data has been split into phases A, B, and C to represent the original process state, transitional process state, and new process state, respectively. The specification limits are shown in blue—note that the original process state is biased towards the upper specification limit.

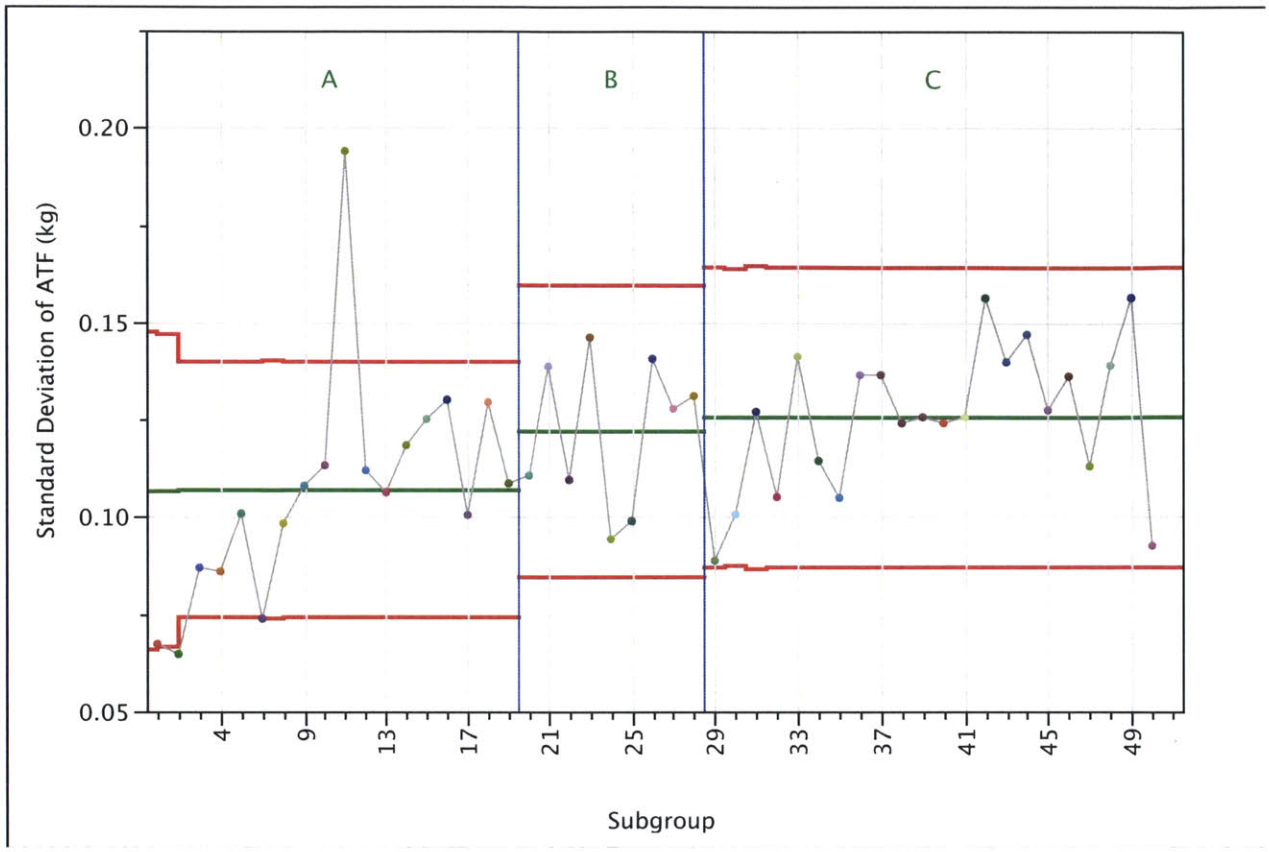

Figure 27. s chart of ATF

A normality check was performed, and individual subgroups appear normal (see Appendix D). The s-chart for the ATF parameter depicted in Figure 27 appears to be reasonably in control within phases A,B, and C. The large spike in phase A is due to an operator error failure, and has been investigated. These results are encouraging, because they indicate the variability within each subgroup is relatively in control. However, the increase in mean standard deviation from Phase A to Phase C indicates that overall subgroup dispersion is increasing. Ideally, the mean standard deviation (indicated by the green line on the graph) would move in the downward direction on the chart. Since the intra-subgroup variability appears to be in control, it makes sense to move on to analyzing inter-subgroup variability via the x-bar chart.

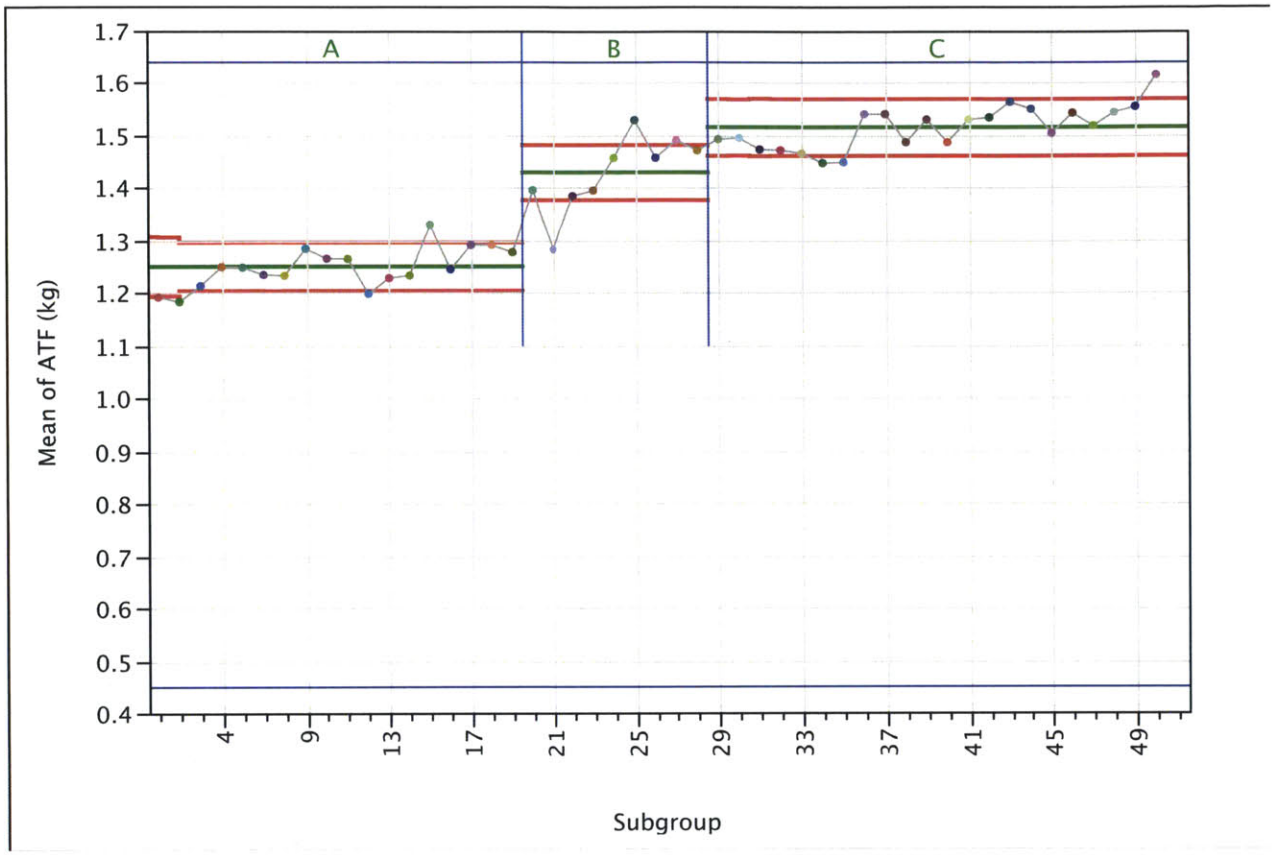

Figure 28. X-bar chart of ATF

The suggested trend that was visible in the original run chart is now quite clear in the x-bar chart in Figure 28. Limits calculated on a 3 sigma basis for each phase are shown in red. Between Phase A and Phase C, a definite process shift has occurred. Since this trend appears to be gradual, a few theories as to the source of variation arise:

- The supplier of the autoinjector components have enacted a process change, resulting Phase B where old and new components were in use and ultimately Phase C where the process has stabilized to the new level.
    - The next step in this investigation is to obtain outgoing testing results from the component supplier. The supplier uses the same SATM to test sampled outgoing autoinjectors before distribution to Amgen—thus it will be beneficial to compare testing results over the transitional period to understand whether they have seen similar results.

- The SATM could potentially be undergoing some form of wear, causing results to gradually trend upwards.
    - Upon investigation, this was found not to be the case. The machine was investigated and still found to be equivalent to the original equipment validation performed and within calibration.

For a data set with a distinct phase shift as shown, it does not make sense to calculate control limits for the entire data set. Instead, control limits should be calculated for the distinct phases. When the control limits are tripped, it is clear that the process is out of control. A corrective action should then be implemented. At that point, new limits should be calculated, set, and monitored for tripping. This is an ongoing cycle as long as the process is shifting. This is the prescient power of the control chart—phase II predicted phase III.

5.6.2 Injection Time (IJT)

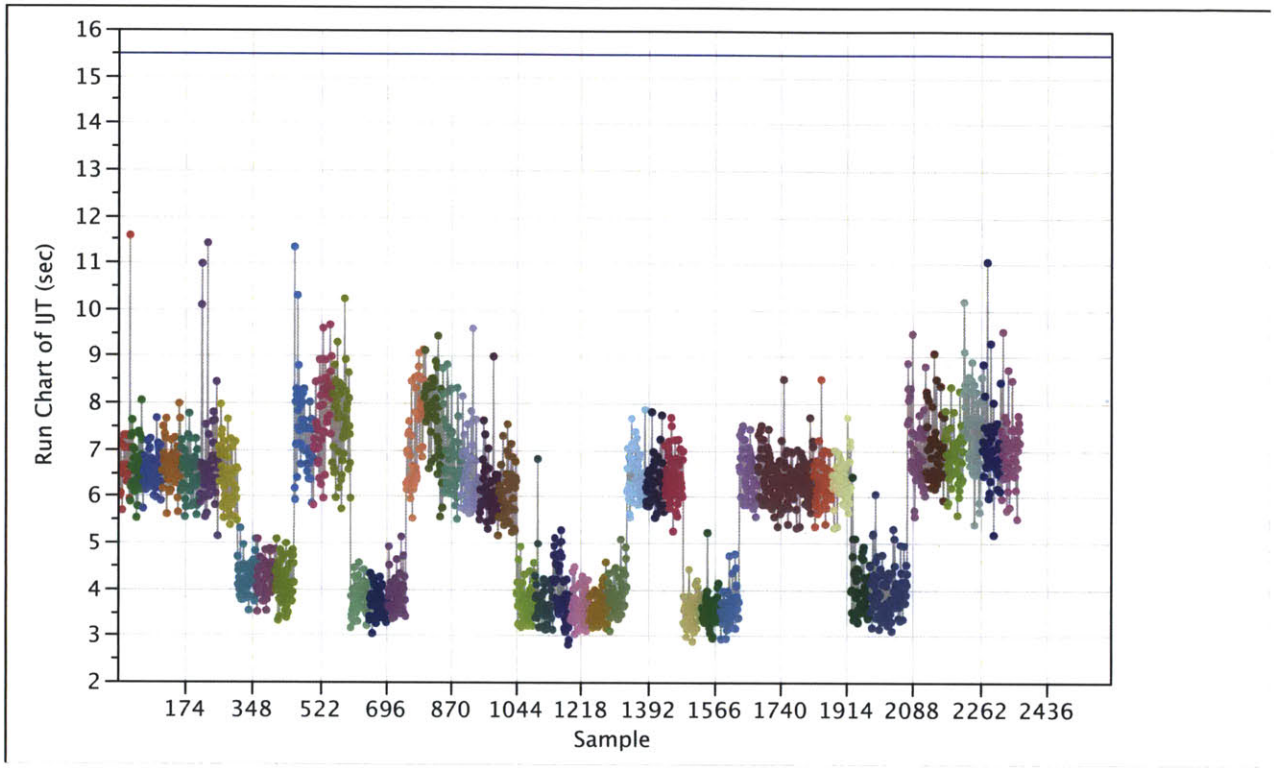

Figure 29. Run chart of IJT (Active and Placebo)

Plotting a basic run chart before any in-depth analysis has been performed has proved useful again. Even without any calculation, it is visibly apparent in Figure 29 that there are two distinct bands of data—the first at approximately 7 seconds and the other at 4 seconds. It is also visible from the groupings of three (beginning, middle, and end) that subgroups from the same batch behave similarly. Upon closer investigation, it was concluded that autoinjectors containing placebo had a faster injection time than autoinjectors containing active drug product. Thus, for the control chart analysis to follow, data is broken out into respective placebo and active graphs. Note that the specification limit for this variable is one sided, and is indicated by the blue line.

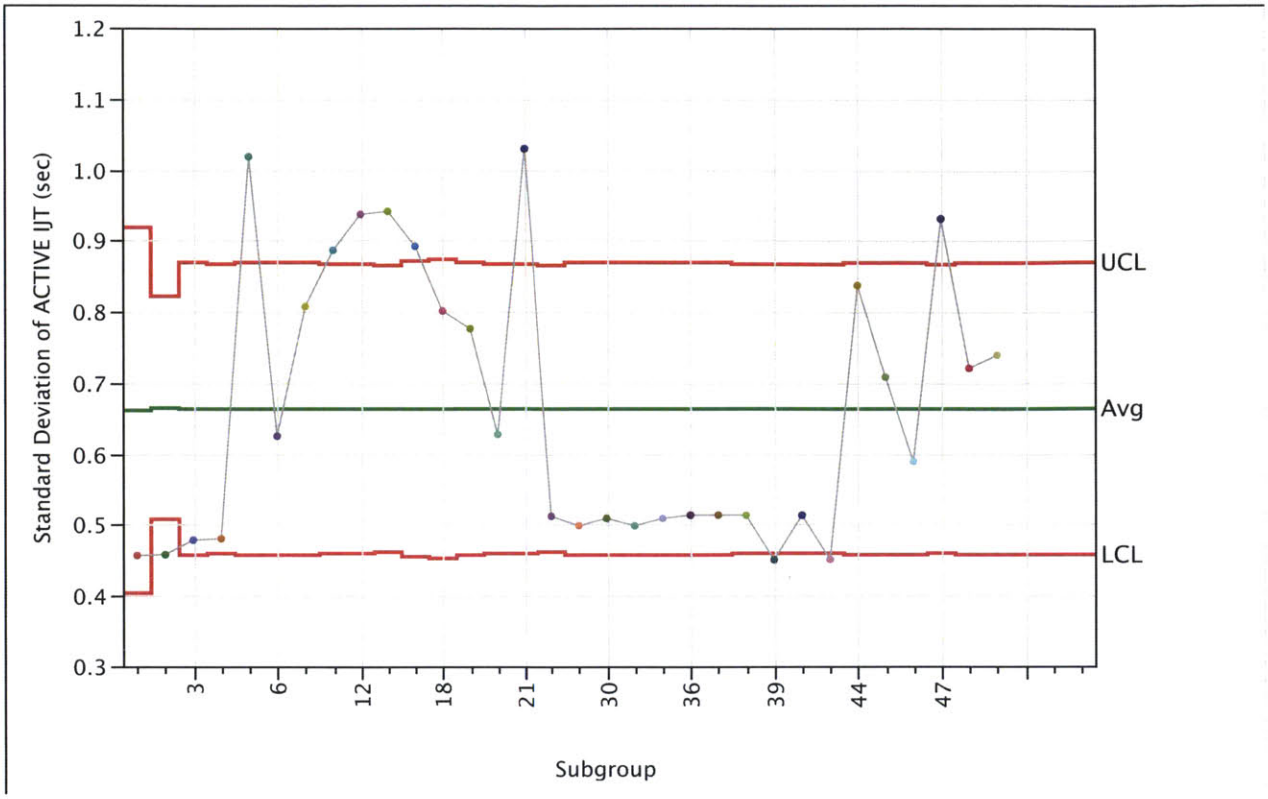

Figure 30. s chart of Active IJT

A normality check was performed, and individual subgroups appear roughly normal (see Appendix D). Unlike activation force, the intra-intra subgroup variability does not appear to be in control in Figure 30. The dispersion of each subgroup appears to be varied and wide.

Before attempting to control variability between subgroups, it is logical to first attempt to control variability within a subgroup.

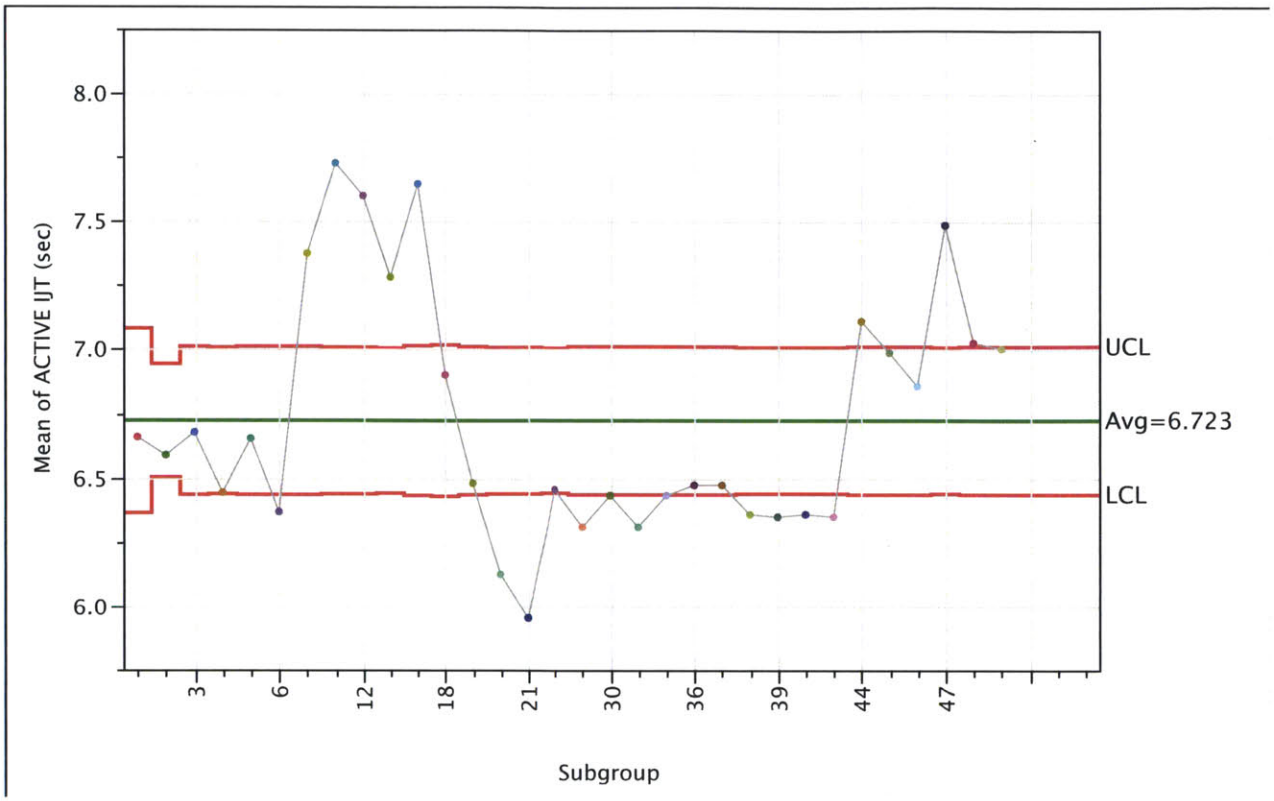

Figure 31. X-bar chart of active IJT

The X-bar chart depicted in Figure 31 implies that variability between subgroups is not in control. As explained above, variability within subgroups should first be within control before attempting to control variability between subgroups. The results for placebo product exhibit very similar characteristics and are included in Appendix E.

Injection time is largely a function of the pre-filled syringe (PFS) that is loaded into the auto-injector and the tolerance on the spring-loaded ejector mechanism in the Rear Assembly of the autoinjector. Recommended investigative actions include:

- Perform a study or obtain vendor data for ejector mechanism to ensure variation is not present
- Consult with upstream drug product team to understand viscosities of product present in the PFS.

From the run-chart, it appears that all of these values are well below the specification limit. It is tempting to assume that the control chart is irrelevant. However it is important to control the variability within the

subgroups and from subgroup to subgroup to ensure that the process is in control and behaving as expected. Significant variations in production can potentially lead to excursions from the specification limits down the line, if left uncontrolled.

5.6.3 Deliverable Volume (DLV)

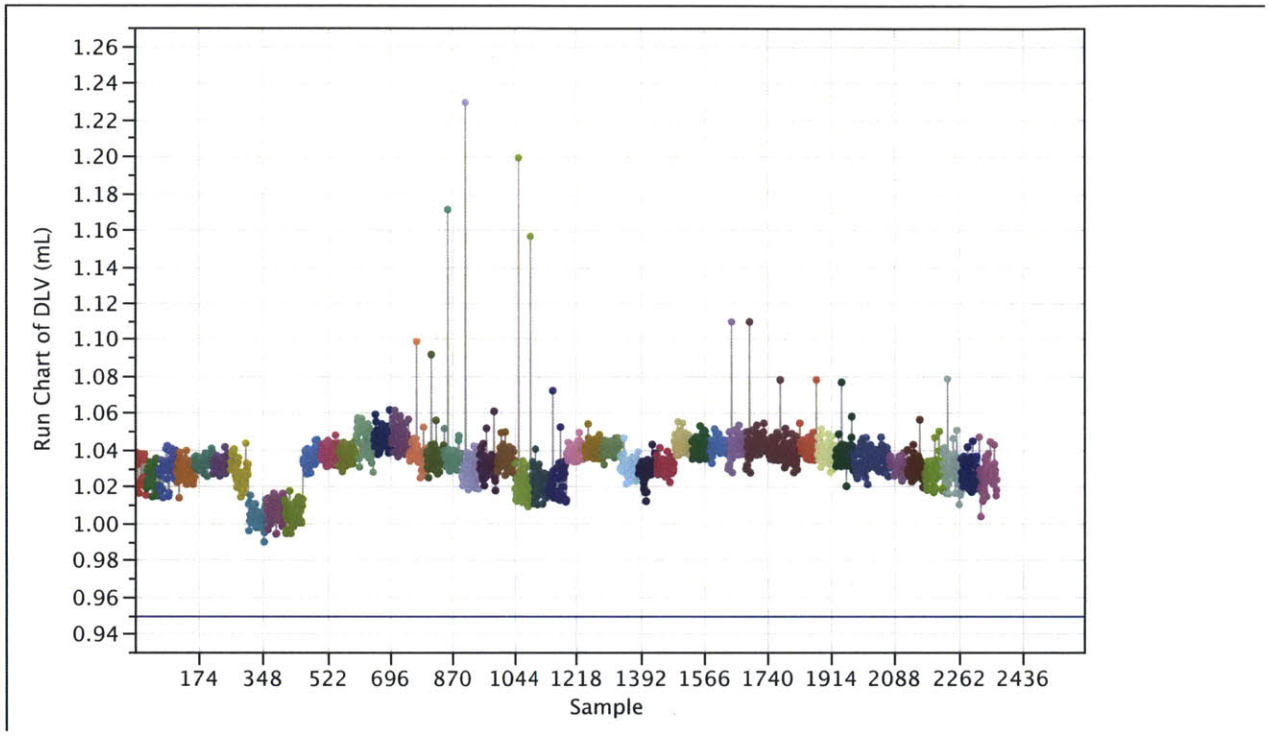

Figure 32. Run chart of DLV

Again, the run chart in Figure 32 provides interesting visual insight. The specification limit, shown in blue, is one sided. There are no significant excursions dipping towards the specification limit, but many excursions away from the specification limit. Although it is positive that there seems to be no danger of failing the specification, these upwards excursions can potentially indicate waste and lowered yields.

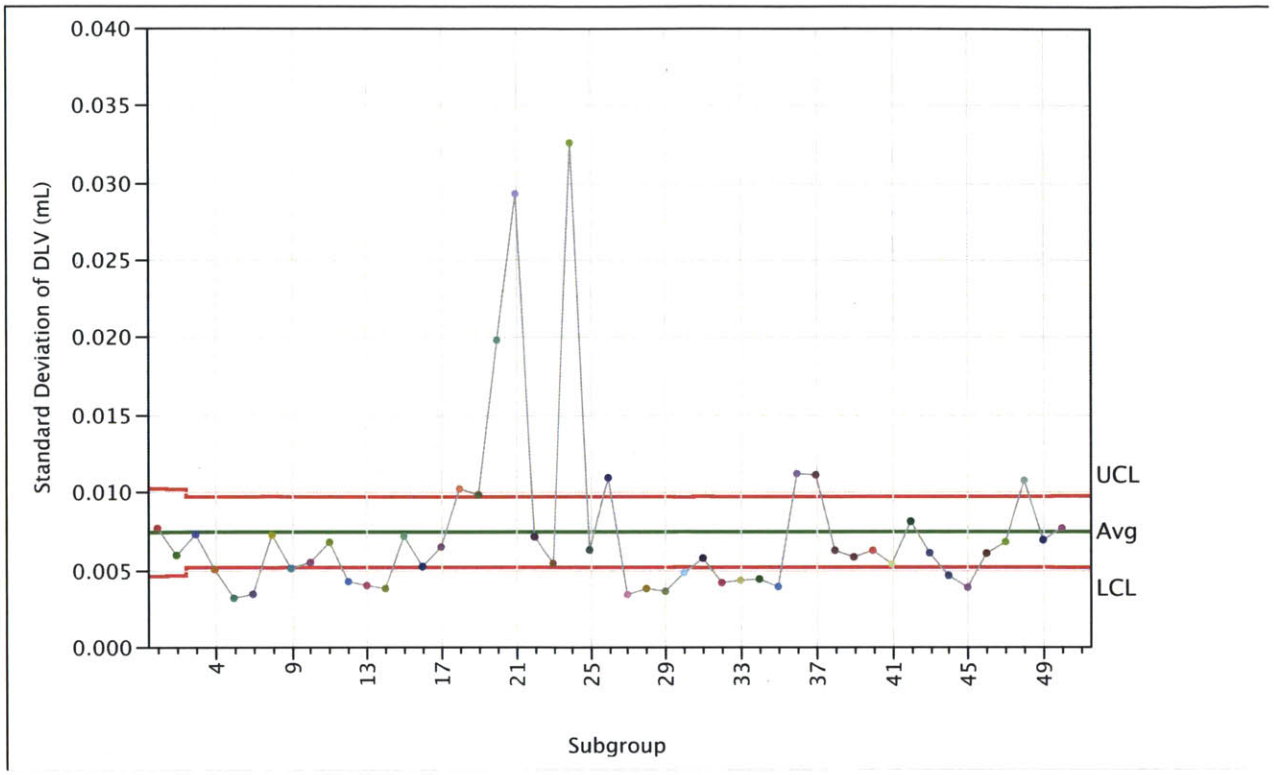

Figure 33. s-chart of DLV

A normality check was performed, and individual subgroups appear roughly normal (see Appendix D). The s chart in Figure 33 indicates that the variability within subgroups is not in control. This confirms the initial suspicion observed in the run chart due to the presence of numerous upwards outliers within individual subgroups.

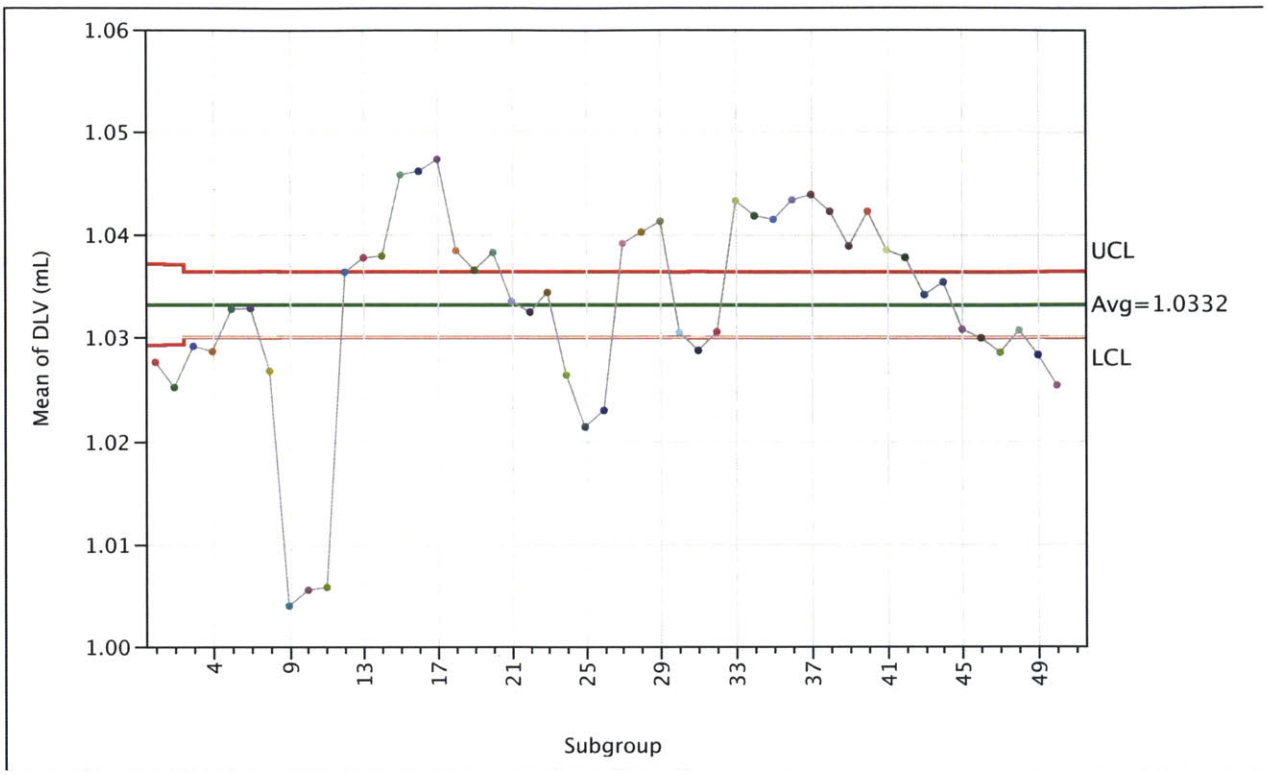

Figure 34. X-bar chart of DLV

The X-bar chart in Figure 34 indicates that variability between subgroups is not in control.

Deliverable volume is solely a function of the PFS. The first step towards attempting to understand the intra-subgroup variability is to analyze upstream data. Syringes are filled in the aptly named Filling Process, and checkweigh data is gathered before transport to the packaging unit to ensure that all syringes are above the specification limit. This variation is indicative of variation upstream of the autoinjector assembly process, and the Filling process must be stabilized to ensure stable results after final assembly.

Again, all points are fairly well above the specification limit. It appears that there is no cause for concern. However, overfilling PFS over time will lead to lowered yields. The clinical drug production team often struggles for yield increases, so overfilling the PFS is an unnecessary waste of product. It is important to bring the process into control in order to ensure the maximum quantities of product.

5.7 Monitoring

Because this data collection and analysis effort occurred at the beginning of the process lifecycle, new data was reviewed often. A cross-functional team consisting of the floor manager, quality representatives, manufacturing representatives, and statistical expert convened weekly to analyze the data. A convenient dashboard was created to analyze the assembly reject data and is shown in Figure 35 below:

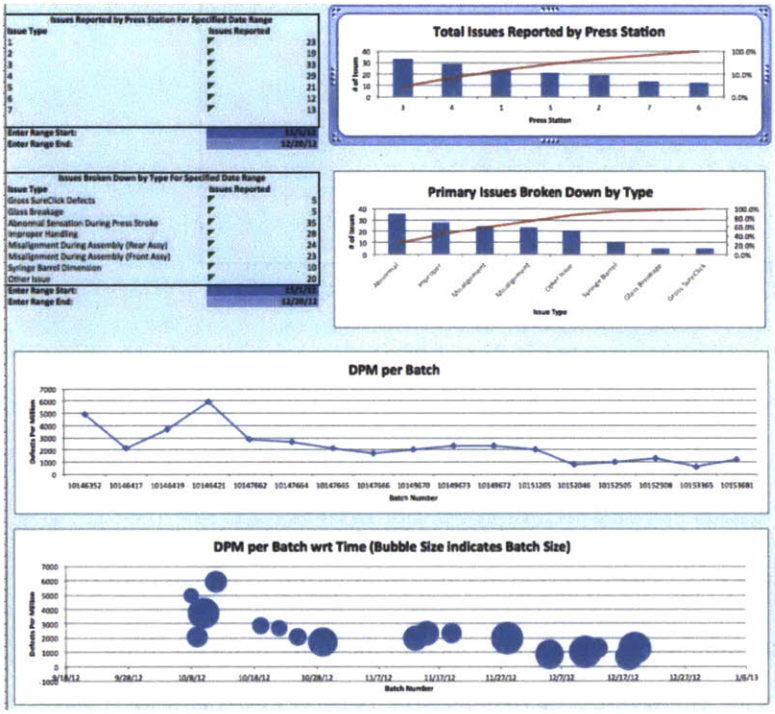

Figure 35. Attribute analysis dashboard

New control charts were generated weekly for the quantitative SATM data, and control limits were discussed. A convenient dashboard was created for automatically analyzing the assembly attribute data. Due to the arduous SATM data collection process, a similar dashboard could not be created for the inspection data. As a result, data from the SATM must be manually formatted and imported to a statistical analysis package. This time consuming collection and analysis of SATM data is currently a significant constraint of the current process. See section 6.1 for specific recommendations.

This meeting serves as an important platform for discussing the state of the process, and the need for potential corrective actions. Although data collection forms the foundation of ITCV, it is equally

important to ensure that the data is presented appropriately and that relevant staff have access to the analysis. At the end of December, it was recommended that in-depth review occur on a monthly basis since the assembly process had largely stabilized.

5.8 Sustainment

5.8.1 Ownership and Accountability

It is important to ensure that a leader for the ITCV program be identified. This owner is then accountable for ensuring data is collected and analyzed, and appropriate review periods are scheduled. A current issue is the existence of multiple quality groups. The clinical packaging group, the drug product manufacturing group, and the combination product devices team all have independent quality groups with some stake in the process. Although these quality groups are united under a senior quality leader, there is ongoing discussion as to where responsibility boundaries should be drawn. Thus designating a clear understanding of ITCV ownership is important to a reliable quality control process.

Additionally it is important to note that integrating quality into manufacturing processes ultimately streamlines quality assurance down the line. ITCV is one example of a method for integrating quality into manufacturing processes. Floor ownership of quality control efforts is also imperative. Cooperation and enthusiasm for the ITCV program was found to significantly increase when data and results were reviewed with the operators. ITCV results are a direct measure or report card for floor operator and floor manager performance. Although upper level managers are interested in ITCV data as a measure of process health, floor operators and floor managers view this data to be a direct assessment of their efforts. Thus, operators and managers were more willing to invest time into ensuring that quality data was collected. It was found that sharing this data with floor staff helped this author make subsequent progress on implementation efforts and make friends.

5.8.2 Training and Documentation

Proper training and documentation is key to the success of ITCV implementation. A pareto analysis of all collected batches is shown in Figure 36. Note that "Other Issue" appears to be the most prevalent category. This can be explained by the first batch of data collected. Instead of taking the time to log each reject with a specific category, operators found it faster to select "Other Issue" without entering any explanatory notes. The electronic data entry form was subsequently modified to mandate an explanatory note if "Other Issue" was selected. As a result, this initial batch has been excluded from all data analysis presented above.

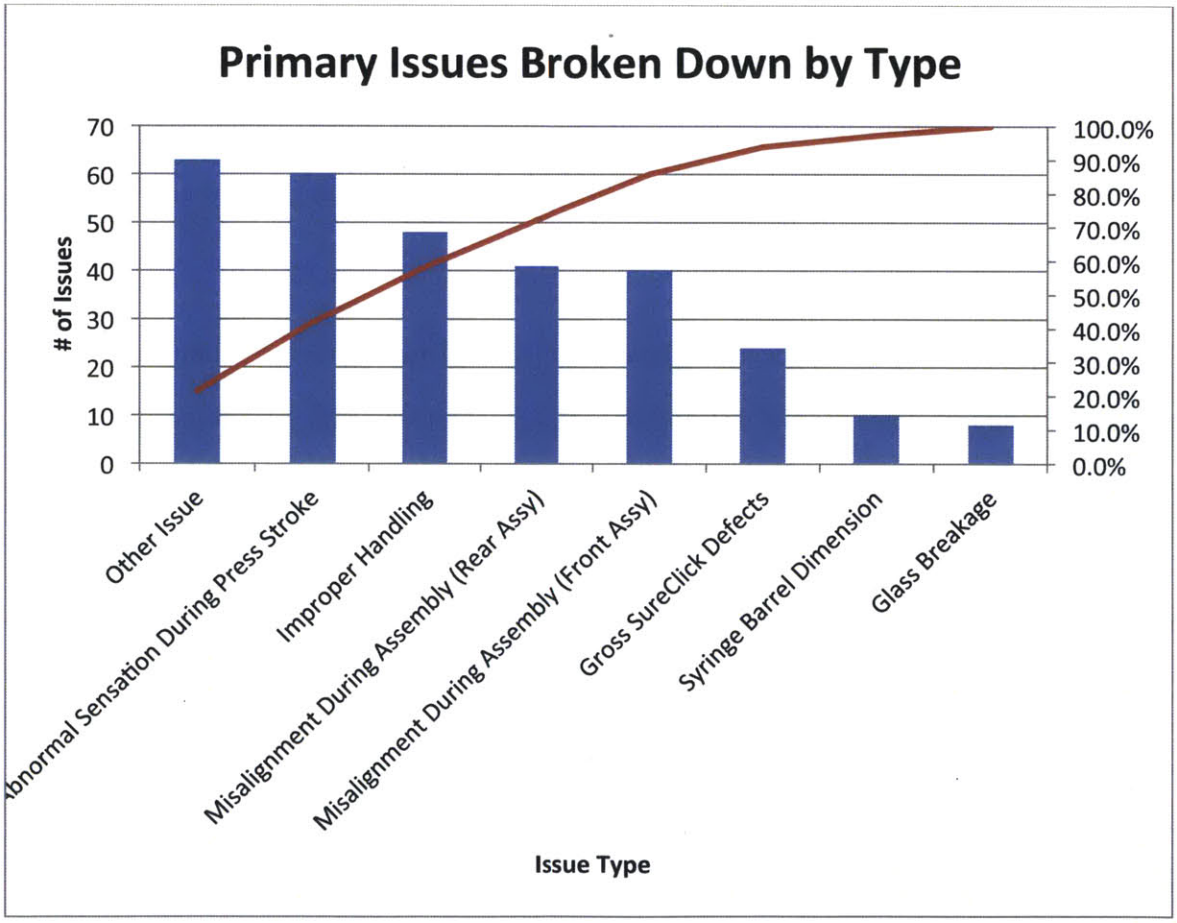

Figure 36. Pareto analysis including data resulting from poor initial training and messaging

This scenario is an example of inadequate change management on the part of this author. It was the responsibility of the author to ensure that this initiative rolled out smoothly – however, all floor operators

were not formally trained regarding the ITCV program before data collection efforts began. Some operators may not have initially understood the purpose of the program, and viewed the extra data logging steps as additional work on top of existing work. Selecting "Other Issue" may have shortened the amount of time an operator would spend logging information. However, with appropriate training, the quality of the data was greatly improved as the operators were informed of the purpose of ITVC. It is essential that operators understand the importance of data collection and analysis. Additionally, a program constraint was added to require entry of a note if "Other Issue" was selected. ITCV is driven by operator compliance, and ultimately, floor operators have the best ability to suggest modifications and improvements to the data collection process.

5.8.3 Continuous Monitoring

Control processes are an ongoing cycle, not an isolated process improvement. It may be tempting to remove control measures after the process appears to be in control; however continuous monitoring is the real power of ITCV. In fact, ITCV and control charts in general are intended as a continuous method of monitoring processes for special causes. It is unknown when a special cause will be introduced, and thus, the process must be monitored continuously.

5.8.4 Data Driven Decision Making

Collection of ITCV data allows Amgen clinical staff to make decisions based on empirical evidence. For example, some units in later lots began to exceed the specification limit for activation force as shown in Figure 26 in section 5.6.1. Instead of wondering if this was due to random error, it was very clear that the process had undergone a gradual shift. This allows Amgen to better pursue a narrow set of causal factors and corrective actions as soon as the issue was discovered. Decision making in the presence of data is always preferable to decision making in the absence of data.

6 Recommendations and Future Work

6.1 Data Collection

A constraint of the program is currently the labor-intensive SATM data collection process. As a nascent process in the clinical organization, it is expected that ITCV will be the first to slip when labor allocation is not sufficient. It is understandable if cost concerns prevent implementation of an IT solution. It is recommended that an analysis should be performed to determine if it is more cost effective to hire a dedicated employee for data collection, or implement a custom IT solution to make the data readily available. However, cost concerns should not rule the day—as Juran indicates, "higher quality costs less, not more [16]." This investment will ensure ITCV ultimately becomes a staple tool in the clinical manufacturing organization.

6.2 Appropriate Organizational Structure

Appropriate organizational support is essential to the survival of the ITCV implementation in the clinical packaging group. As with the change management of any new quality process rollout in any organization, it is important to assess the tradeoffs of personnel and equipment allocation and the expected advantage of the outcome. A business case must be built in support of the new process rollout, and a change management plan outlined. However, it should be analyzed as a part of the business case that additional staff may be paid for out of reduction of quality losses [16]. Despite the fact that the clinical manufacturing organization does not generate revenue, costs are still a concern to the broader organization.

Beyond this implementation of ITCV, it is advantageous to dedicate some portion of the staff to clinical process control improvement. Currently, the clinical packaging team runs at full capacity, with little time for anything beyond day-to-day responsibilities. It is also important to ensure that the organizational

structure of the ITCV support team includes staff with the statistical know-how to manage the recurring activities of process control.

As mentioned earlier, it is important to define boundaries between the various quality groups in the clinical space. The additional resource advocated in the paragraph above would need to interface with the other quality groups to ensure that the process is clear to all involved and that drug product, medical device, and final assembly teams all act in concert. This type of engagement also fosters teamwork and goodwill. However, successful implementation of quality into clinical manufacturing processes will ultimately make the precise organizational structure of quality groups less relevant—quality will be built into the process. ITCV is part of this effort in the clinical organization.

6.3 Periodic Review

This project has reached a state where it has been identified that not all processes are in statistical control—it is important to continue to collect data and make corrective actions until all process are in control. Thus periodic review by a cross-functional team is important. This team should have the authority to pursue process improvements and corrective actions, in addition to having the statistical background to understand the data analysis.

6.4 Scope

ITCV can span as an integrated control system from raw material receipt to distribution within the clinical manufacturing organization. This body of process data is a valuable package to hand over to commercial manufacturing teams when a product transitions out of the clinical organization. This process data can be used by commercial manufacturing as a platform upon which to build process excellence, instead of starting from scratch. Due to the high stakes in the commercial manufacturing environment, quality failures have significant costs and regulatory consequences. Ultimately, the potential for the commercial manufacturing environment to learn from past issues in the clinical production environment may prove more valuable to Amgen than any particular quality savings in the clinical production space.

ITCV also has the potential to become a corporate process quality tool. As mentioned at the beginning of this thesis, Amgen's strength lies in the workforce's "quality mindedness." However, a common program of statistical process control tools is missing from team to team within the clinical manufacturing organization. By standardizing methods of process improvement and process control, the "quality mindedness" of staff can only increase. It is hoped that widespread adoption of ITCV can fill this gap and serve as a common tool for process improvement in the clinical organization.

6.5 Conclusions

Although the process control techniques utilized in this implementation are not novel, the impact they have had on Amgen's clinical manufacturing environment has been measurable and real. In fact, these techniques are older than Amgen, biologics manufacturing, and the FDA itself. It is astonishing to understand that techniques developed a century ago are still relevant in today's modern era. The original formulation of this thesis has more than been proven by producing real time indicators of process health illustrating the ability to use today's data to predict tomorrow's events. This ability is invaluable to any type of manufacturer.

It is important for Amgen to understand that ITCV merely serves as a platform for process improvement. Amgen has enjoyed significant margins and comfortable revenues in the past era, however with patent expiry and health care cost reductions on the horizon, it is more important than ever for Amgen to focus on the bottom line. ITCV is a perfect tool for introducing the power of systemic process improvement to Amgen's clinical manufacturing centers. This basic implementation will hopefully serve as a launching point for an organized campaign of quality control and process improvement to further Amgen's clinical operation excellence.

7 References

[1] Juran, J. M. Quality Control Handbook. New York: McGraw-Hill Book Company, 1962. Print. (p10-15)

[2] CFR Title 21, Subchapter F, Part 600, Sec 3 (h)

[3] Amgen 2011 Annual Report.

[4] CFR Title 21, Subchapter A, Part 3, Sec 2 (e)

[5] "Current Good Manufacturing Practice for Combination Products (Draft Guidance)." fda.gov. n.p. Web. September 2004.

[6] http://www.shl-group.com/en/products/shl-medical/disposable-autoinjector.html

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[10] Ott, Ellis R, Schilling, Edward G, Neubauer, Dean V, *Process Quality Control: Troubleshooting and Interpretation of Data. Fourth Edition.* Milwaukee: ASQ Quality Press: 2005. Print. (p195)

[11] Ott, Ellis R, Schilling, Edward G, Neubauer, Dean V, *Process Quality Control: Troubleshooting and Interpretation of Data. Fourth Edition.* Milwaukee: ASQ Quality Press: 2005. Print. (p197)

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[13] Doty, Leonard. SPC for Short Run Manufacturing. Cincinnati: Hanser Gardner Publications, 1997. Print. (p98)

[14] Juran, J. M. Quality Control Handbook. New York: McGraw-Hill Book Company, 1962. Print. (p6-41)

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[16] Juran, J. M. Quality Control Handbook. New York: McGraw-Hill Book Company, 1962. Print. (p6-35)

[17] http://www.buec.udel.edu/kherh/table_of_control_chart_constants.pdf

8 Appendix A

Table of Control Chart Constants [17]

Sample Size = m	A_2	A_3	d_2	D_3	D_4	B_3	B_4
2	1.880	2.659	1.128	0	3.267	0	3.267
3	1.023	1.954	1.693	0	2.574	0	2.568
4	0.729	1.628	2.059	0	2.282	0	2.266
5	0.577	1.427	2.326	0	2.114	0	2.089
6	0.483	1.287	2.534	0	2.004	0.030	1.970
7	0.419	1.182	2.704	0.076	1.924	0.118	1.882
8	0.373	1.099	2.847	0.136	1.864	0.185	1.815
9	0.337	1.032	2.970	0.184	1.816	0.239	1.761
10	0.308	0.975	3.078	0.223	1.777	0.284	1.716
11	0.285	0.927	3.173	0.256	1.744	0.321	1.679
12	0.266	0.886	3.258	0.283	1.717	0.354	1.646
13	0.249	0.850	3.336	0.307	1.693	0.382	1.618
14	0.235	0.817	3.407	0.328	1.672	0.406	1.594
15	0.223	0.789	3.472	0.347	1.653	0.428	1.572
16	0.212	0.763	3.532	0.363	1.637	0.448	1.552
17	0.203	0.739	3.588	0.378	1.622	0.466	1.534
18	0.194	0.718	3.640	0.391	1.608	0.482	1.518
19	0.187	0.698	3.689	0.403	1.597	0.497	1.503
20	0.180	0.680	3.735	0.415	1.585	0.510	1.490
21	0.173	0.663	3.778	0.425	1.575	0.523	1.477
22	0.167	0.647	3.819	0.434	1.566	0.534	1.466
23	0.162	0.633	3.858	0.443	1.557	0.545	1.455
24	0.157	0.619	3.895	0.451	1.548	0.555	1.445
25	0.153	0.606	3.931	0.459	1.541	0.565	1.435

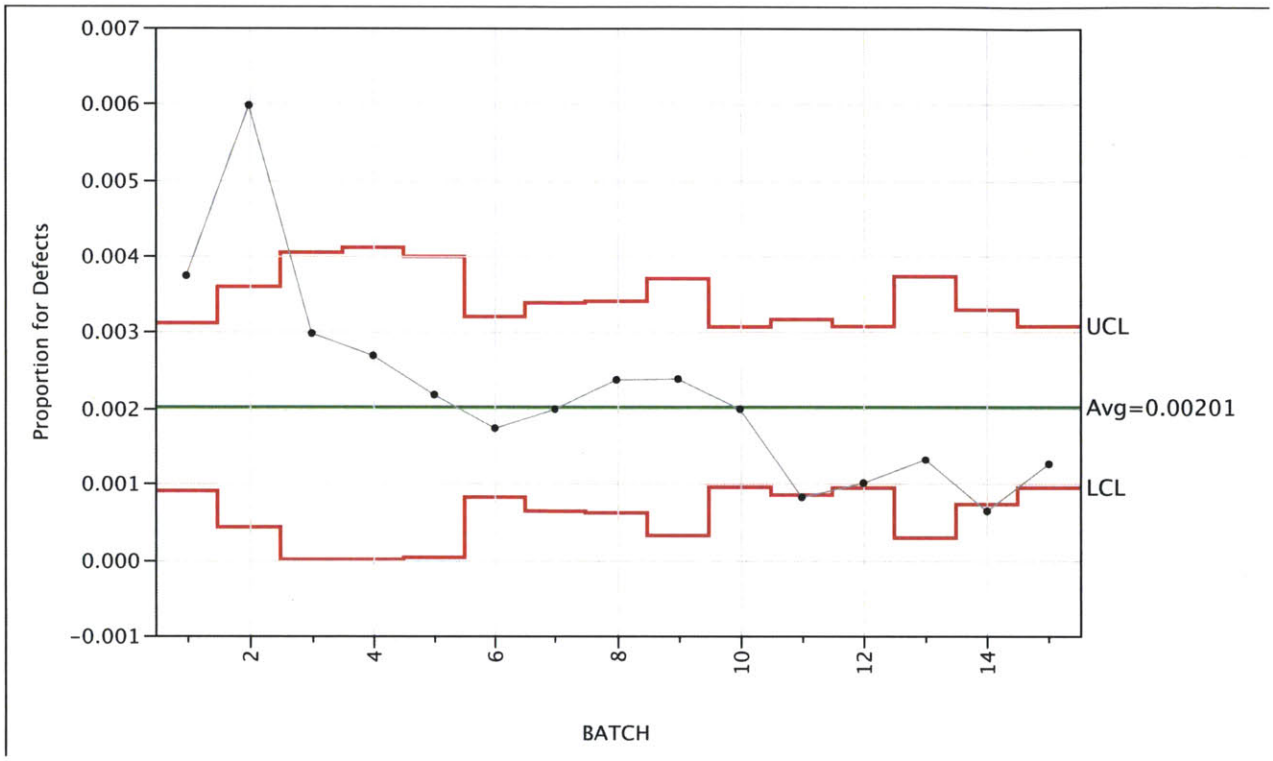
9 Appendix B

ID	Applies to	Process Step	Equipment	Characteristics		Measurement Methods					Controls				
No.	Default = "General" or Define specific SKU, product or packaging configuration	process step name / description	machine, device, tool, etc.used in the step (incl. equip # where applicable)	process characteristic (defines the relevant controllable parameter of the equipment / process)	Description	Performance Evaluation Parameter	Trend Evaluation Method	data source (batch record, form, electronic data capture, etc.)	Data Frequency	Review frequency	product / process spec	control limits		operator process instructions (procedure #)	reaction if out of control conditions are encountered
												LCL	UCL		
1	**Clinical Autoinjector**	Manual Observation	Operator	Gross Autoinjector Defect	Scratches, cosmetic defects, broken Autoinjector components	TBD: PPM	Histogram	Data Entry Spreadsheet	Per Batch	Per Batch	Excluded	N/A	N/A	Excluded	TBD
2	**Clinical Autoinjector**	Manual Observation	Operator	Glass Breakage	Broken Syringe	TBD: PPM	Histogram	Data Entry Spreadsheet	Per Batch	Per Batch	Excluded	N/A	N/A	Excluded	TBD
3	**Clinical Autoinjector**	Manual Observation	Operator	Abnormal Sensation During Press Stroke	Unusual proprioceptive feel during manual press stroke step	TBD: PPM	Histogram	Data Entry Spreadsheet	Per Batch	Per Batch	Excluded	N/A	N/A	Excluded	TBD
4	**Clinical Autoinjector**	Manual Observation	Operator	Improper Handling	Dropped syringe, or dropped Autoinjector containing syringe	TBD: PPM	Histogram	Data Entry Spreadsheet	Per Batch	Per Batch	Excluded	N/A	N/A	Excluded	TBD
5	**Clinical Autoinjector**	Manual Observation	Operator	Misalignment During Assembly (Rear Assy)	Misalignment during first press step	TBD: PPM	Histogram	Data Entry Spreadsheet	Per Batch	Per Batch	Excluded	N/A	N/A	Excluded	Conduct investigation and escalate to Product Team
6	**Clinical Autoinjector**	Manual Observation	Operator	Misalignment During Assembly (Front Assy)	Misalignment during second press step	TBD	Histogram	Data Entry Spreadsheet	Per Batch	Per Batch	Excluded	N/A	N/A	Excluded	Conduct investigation and escalate to Product Team

ID	Applies to	Process Step	Equipment	Characteristics		Measurement Methods					Controls				
No.	Default = "General" or Define specific SKU, product or packaging configuration	process step name / description	machine, device, tool, etc. used in the step (incl. equip # where applicable)	process characteristic (defines the relevant controllable parameter of the equipment / process)	Description	Performance Evaluation Parameter	Trend Evaluation Method	data source (batch record, form, electronic data capture, etc.)	Data Frequency	Review frequency	product / process spec	control limits		operator process instructions (procedure #)	reaction if out of control conditions are encountered
												LCL	UCL		
7	**Clinical Autoinjector**	Manual Observation	Operator	Syringe Barrel Dimension too Large	Syringe falls off press because syringe dimension is not adequate	TBD	Histogram	Data Entry Spreadsheet	Per Batch	Per Batch	Excluded	N/A	N/A	Excluded	Conduct investigation and escalate to Product Team
8	**Clinical Autoinjector**	Functional Testing	Semi Automatic Testing Machine (SATM)	Deliverable Volume (DLV)	Volume delivered during activation	Excluded	Control Chart	SATM-Manual Data Capture	Each Batch Portion	Per Batch	Excluded	TBD	TBD	Excluded	Conduct investigation and escalate to Product Team
9	**Clinical Autoinjector**	Functional Testing	Semi Automatic Testing Machine (SATM)	Injection Time (IJT)	Length of delivery time	Excluded	Control Chart	SATM-Manual Data Capture	Each Batch Portion	Per Batch	Excluded	TBD	TBD	Excluded	Conduct investigation and escalate to Product Team
10	**Clinical Autoinjector**	Functional Testing	Semi Automatic Testing Machine (SATM)	Activation Force (ATF)	Force required to activate unit	Excluded	Control Chart	SATM-Manual Data Capture	Each Batch Portion	Per Batch	Excluded	TBD	TBD	Excluded	Conduct investigation and escalate to Product Team
11	**Clinical Autoinjector**	Functional Testing	Needle Extension Gauge	Needle Extension (IJD)	Length of Needle Extension	Excluded	Control Chart	Laptop-Manual Data Capture	Each Batch Portion	Per Batch	Excluded	TBD	TBD	Excluded	Conduct investigation and escalate to Product Team
12	**Clinical Autoinjector**	Yield	Batch Record	Ratio batch size to components used	Reject Rate	% Accepted	Run Chart	EBR	Per Batch	Per Batch	Excluded	N/A	N/A	Excluded	Conduct investigation and escalate to Product Team

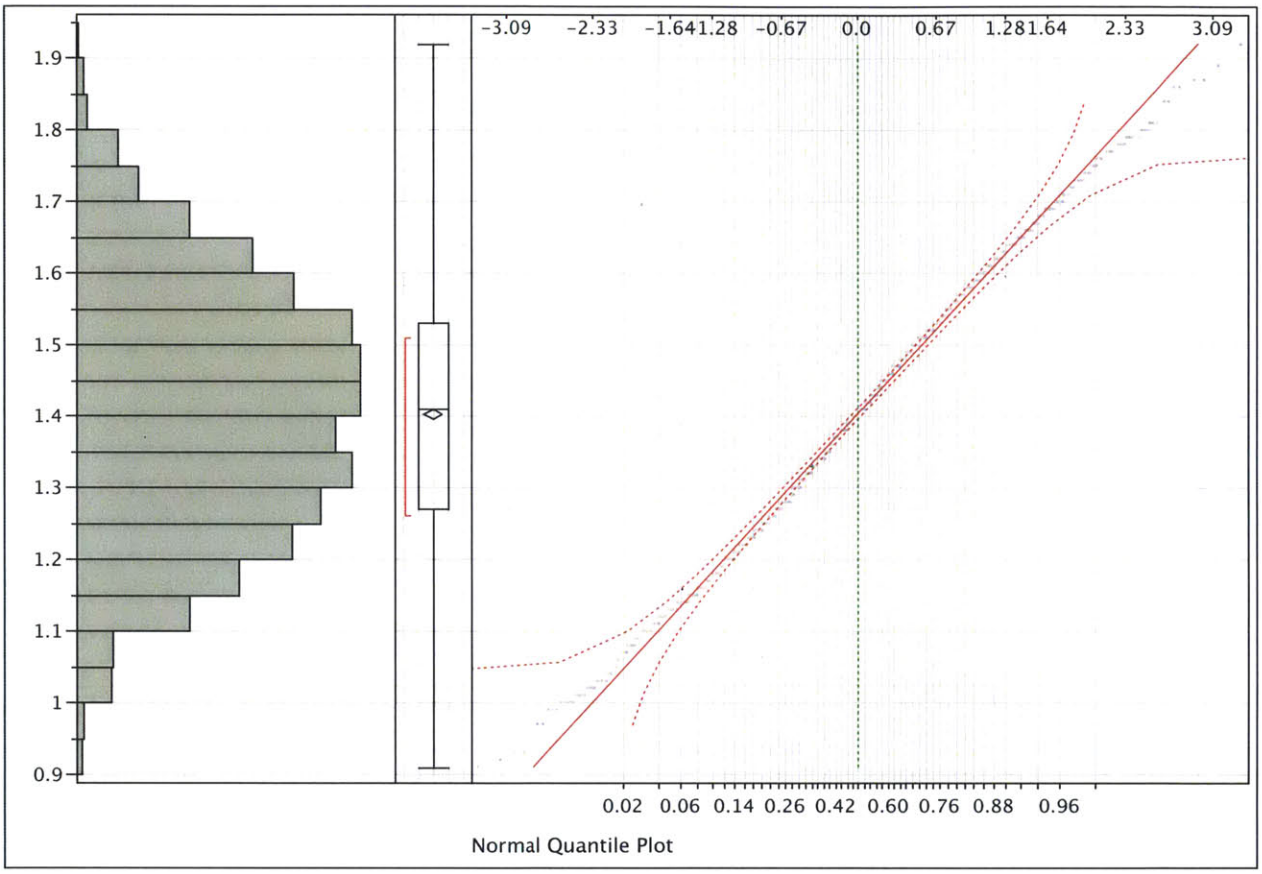
10 Appendix C

P chart of defects: control limits are distracting due to varying autoinjector build size.

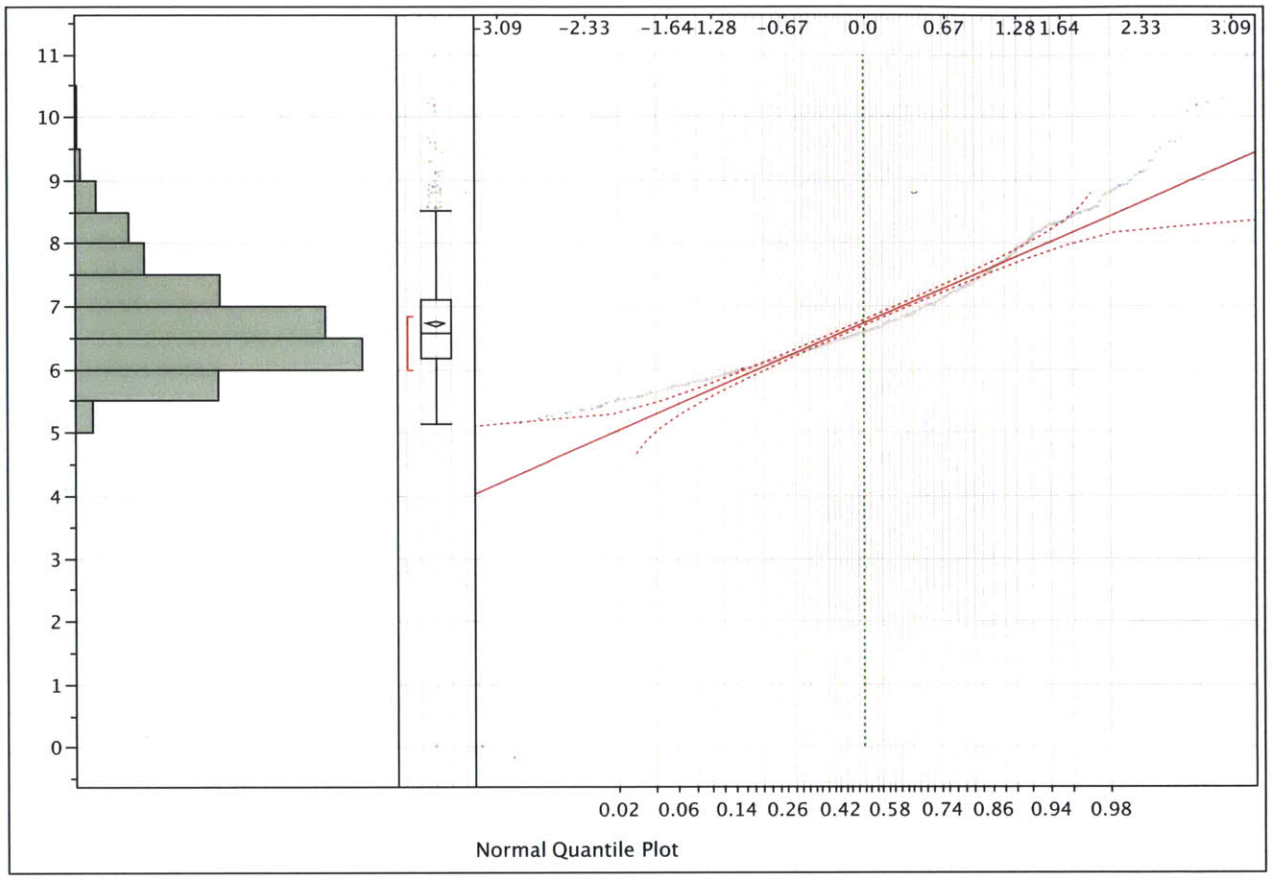


11 Appendix D

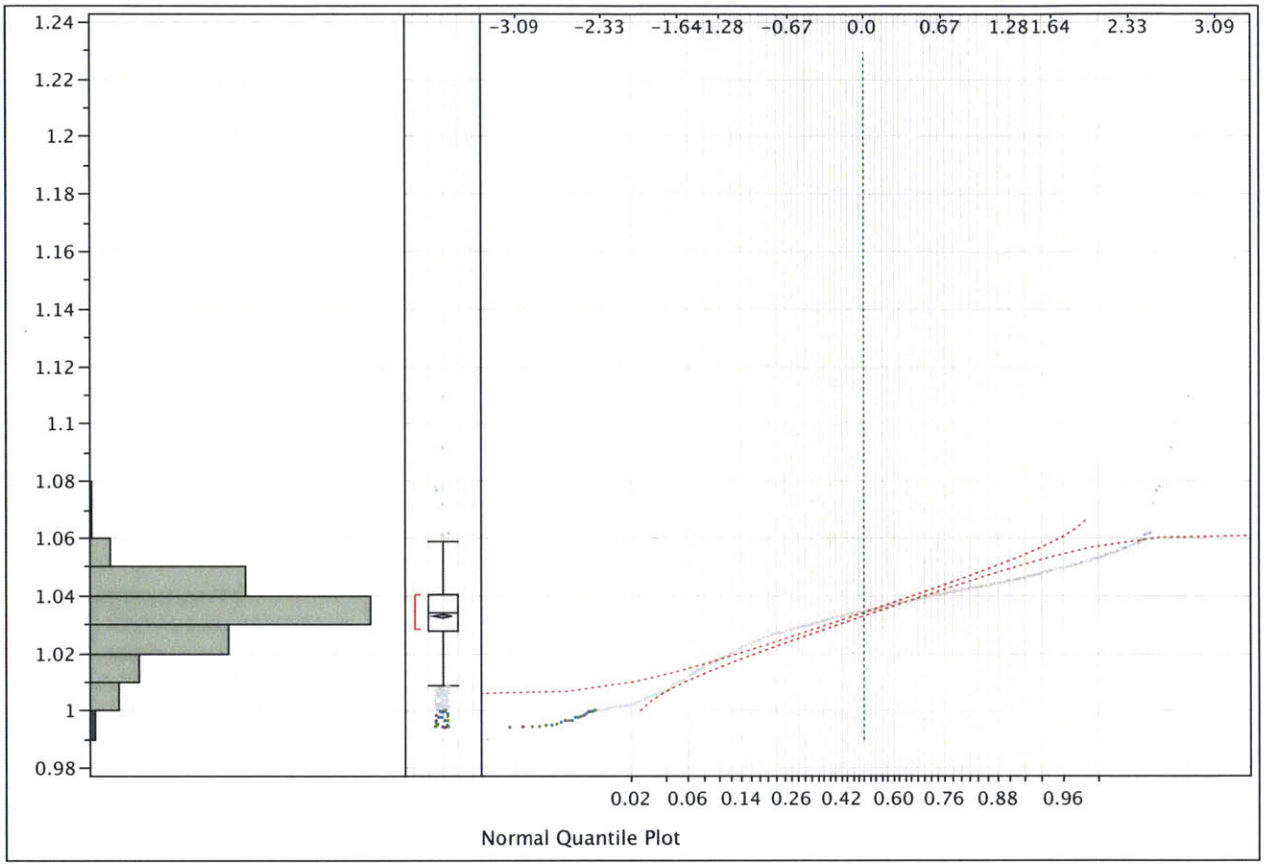
ATF Normality Check



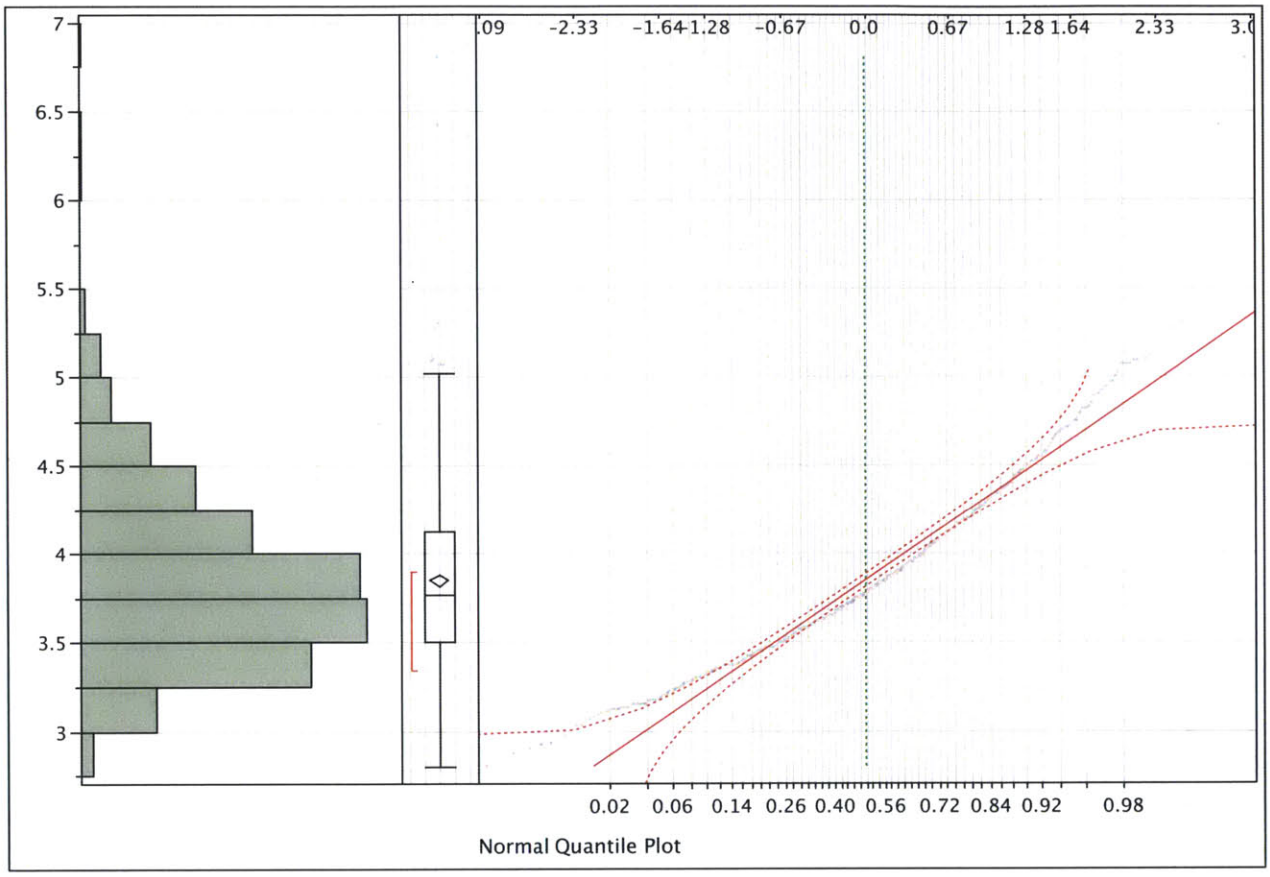
IJT (Active) Normality Check



DLV Normality Check

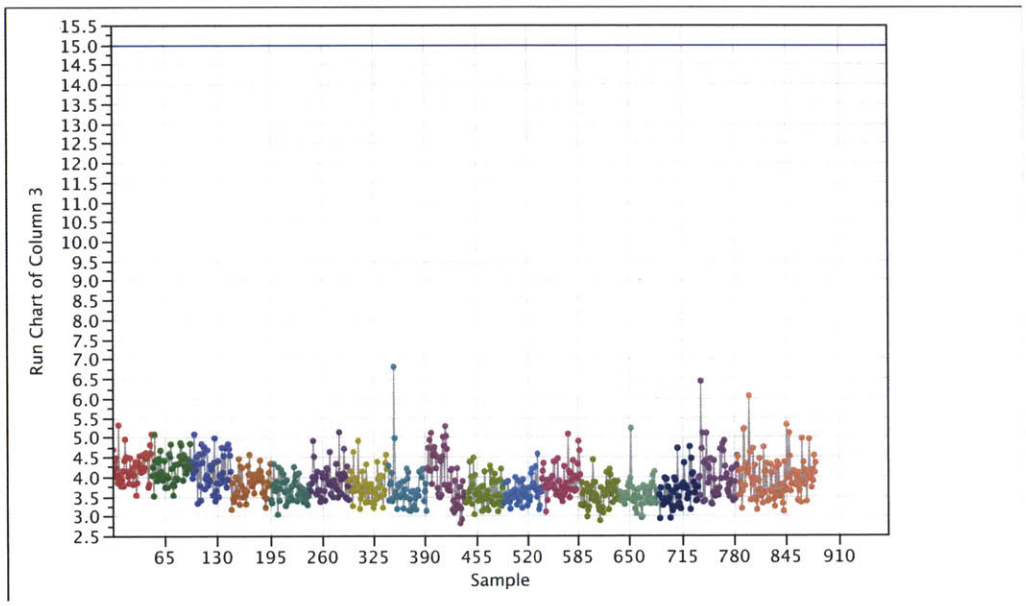


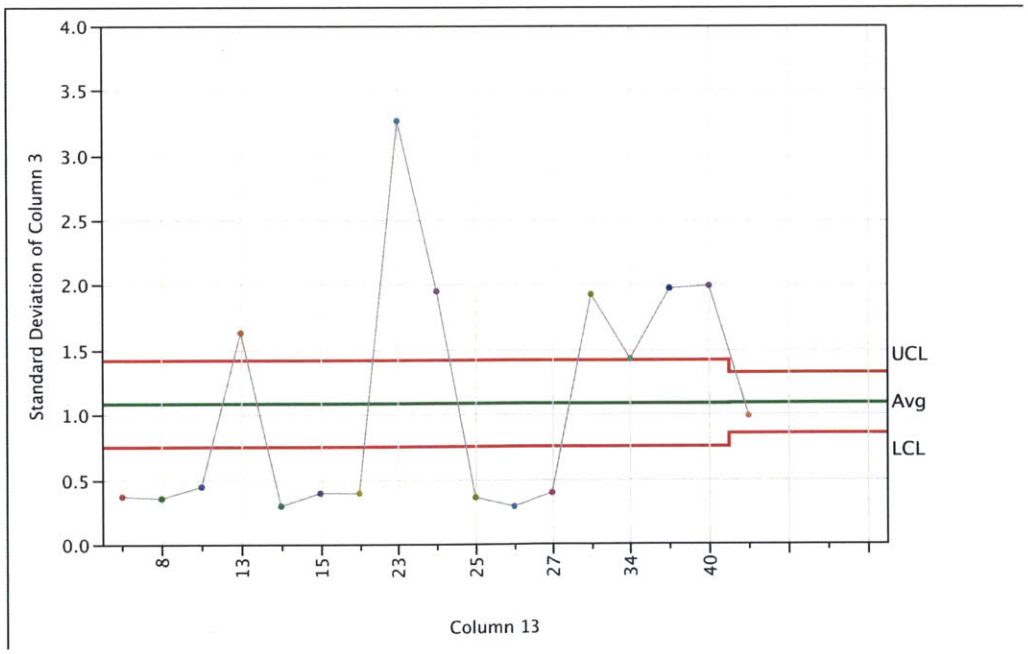
IJT (Placebo) Normality Check

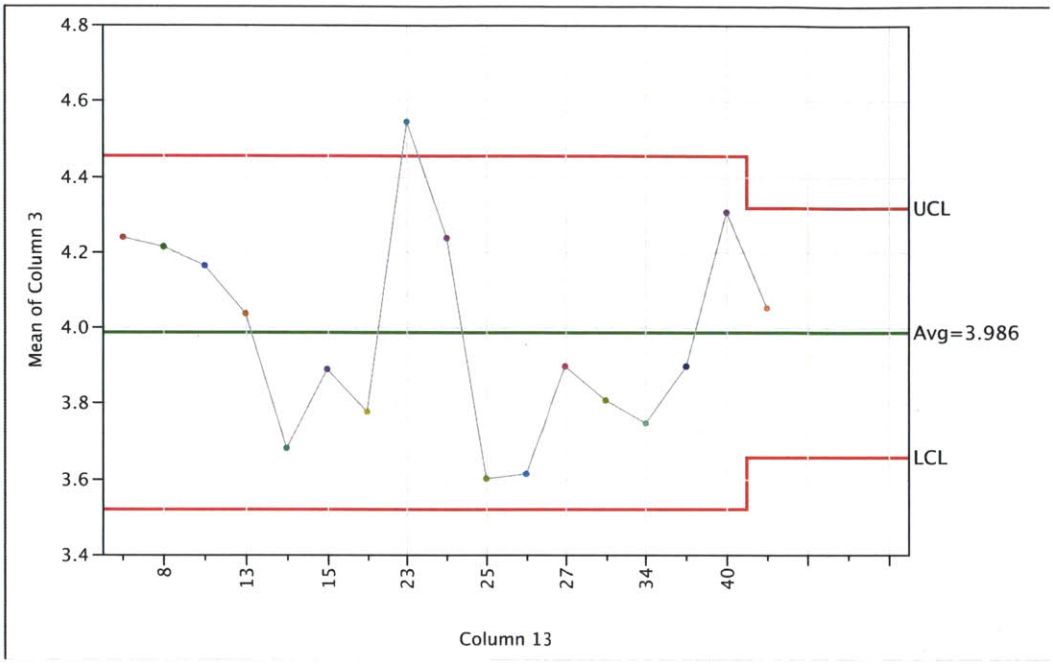


12 Appendix E

IJT Placebo Analysis



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4.6
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3.8
3.6
3.4
Mean of Column 3
UCL
Avg=3.986
LCL
8
13
15
23
25
27
34
40
Column 13